Moderate prematurity, socioeconomic status, and neurodevelopment in early childhood

A life course perspective

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Colofon

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If we had no winter, the spring would not be so pleasant: if we did not sometimes taste of adversity, prosperity would not be so welcome

– Anne Bradstreet –

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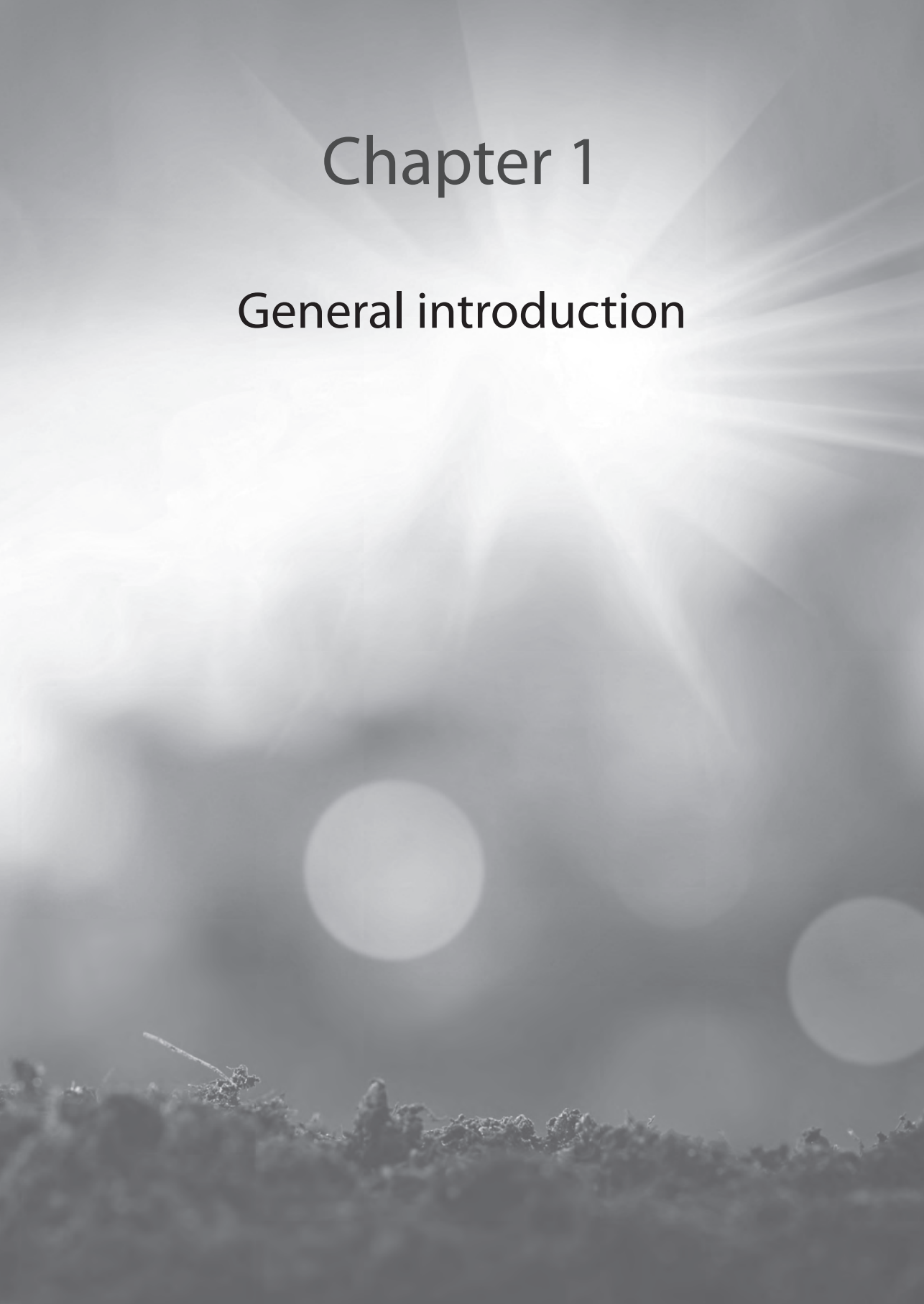
Chapter 1

General introduction



In foetal life and in early childhood, rapid developmental processes in the central nervous system[1] enable a child to adapt to the demands of the environment. However, if children are exposed to early adversities, such as preterm birth and low socioeconomic status (SES), the normal neurodevelopmental processes may come under threat. Early adversities may cause permanent changes in brain and body functions, potentially affecting the foundations of mental and physical health. The main aim of this thesis was to determine the associations between moderate to late prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective.

BACKGROUND

Moderate prematurity

Worldwide, approximately 10% of live births are preterm, that is birth before 37 weeks of gestation.[2] Of the 12.9 million children concerned,[2, 3] up to 85% are born between 32 and 37 weeks of gestation. Children born within this gestational age-range are referred to as moderately preterm (MP) and late preterm. In the Netherlands, approximately 10,000 births per year are within this age range.[4] Due to the large number of children involved, MP and late preterm-born children contribute substantially to the societal burden associated with preterm birth.[5, 6] By contrast, the individual burden is higher in very preterm children (born before 32 weeks' gestation), as the risks of mortality and morbidity are much higher.[7] Therefore, up to fifteen years ago researchers were particularly interested in outcomes following very preterm birth, but we now know that MP children too face significantly more neonatal and developmental problems than full-term children do.[8] Examples of neonatal morbidities occurring in MP and late preterm-born children are temperature instability and hyperbilirubinemia, which often lead to a longer stay in hospital.[9-11] Furthermore, in the longer term, MP and late preterm-born children have an increased risk of developmental and neurobehavioral problems, such as developmental delay,[12] and social and functional difficulties at school age.[13-15] In the following paragraphs, we describe what is currently known about developmental outcomes, as well as behavioural and emotional outcomes in MP children.

Developmental outcomes

The risk of developmental delay in four-year-old, MP children is twice that of full-term children and half that of very preterm-born children.[12] Developmental delay refers to a condition in which a child has not achieved one or more skills, or 'milestones', at the age at which most other children have reached these particular milestones. Prevalence rates of developmental delay increase exponentially with decreasing gestational age, as depicted in Figure 1.[16] In MP children the prevalence varies from 6% to 11% for gestational weeks 32 to 36, compared to 4% on average in full-term children.[16] More specifically, we found that MP children show more delay in fine motor, communication, problem-solving, and personal-social functioning at preschool age.[12] Later on, developmental impairments may continue to cause problems at primary school, as they may lead to poor handwriting and difficulties in motor coordination and verbal fluency.[17-19] Furthermore, MP children frequently lag behind their peers in executive functioning, attention, and visuospatial reasoning.[20]

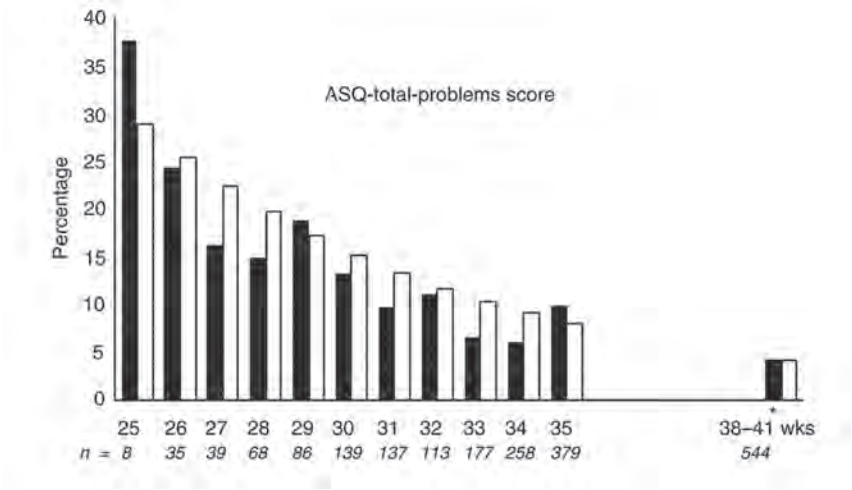


Figure 1 Exponential association between gestational age and developmental delay (i.e. abnormal total-problems score on the Ages and Stages Questionnaire, ASQ). The white bars depict the expected percentages of developmental delay according to an exponential model. The black bars depict the real percentages. Adapted from Kerstjens et al.[16]

Behavioural and emotional outcomes

Recent insights showed that developmental and behavioural and emotional disabilities have bumped physical disabilities from the throne as the leading cause of daily limitations in children.[21] From early childhood onwards, prevalence rates of behavioural and emotional problems gradually increase, rising from 5% up to as high as 40% in adolescence,[22-24] with a high risk of persisting into adulthood.[24-26] Behavioural and emotional problems have an impact on the developmental and social competencies of children, both at school and in the community at large.[25, 27, 28]

Evidence concerning behavioural and emotional outcomes among MP children is limited compared to the wealth of articles reporting on these outcomes in very preterm-born and/or children with low birth weight.[29, 30] In a Dutch study, 13% of five-year-old, very preterm-born and/or children with low birth weight had clinical-range behavioural and emotional problems, as measured by the Child Behavior Checklist (CBCL).[23] As is the case in full-term girls and boys, preterm girls also tend to have more emotional problems, such as withdrawn behaviour, while preterm boys tend to have more externalizing problems, especially attention problems.[23, 29, 31]

Studies on behavioural and emotional problems in MP and late preterm-born children have shown conflicting results, although most studies did find that behavioural and emotional problems occurred more often in MP children, particularly regarding attention and internalizing problems.[32, 33] Conversely, one study showed no differences in externalizing, internalizing, aggressive, and anxious/depressed problems in comparison to full-term children.[34] The studies mentioned here, however, included relatively small samples of MP and late preterm-born children, or they lacked a control group of full-term children. Moreover, evidence on early emerging behavioural and emotional problems in preschool-aged children is very limited. In summary, there is a need for larger cohort studies on MP children in order to assess the full range of behavioural and emotional problems at pre-school age. These studies should include full-term control groups.

Co-occurrence of developmental and behavioural problems

The presence of co-occurring developmental and behavioural problems in early childhood increases the risk of psychiatric disorders at older ages considerably.[35-37] Children with developmental delay are much more likely to have co-occurring behavioural and emotional problems than children without developmental delay. A combination frequently seen is motor problems, such as coordination

problems, co-occurring with attention-deficit/hyperactivity disorder. The origin of co-occurring problems is still unclear. In some cases, the behavioural problems may be caused by the underlying developmental delay.[38] Children with language problems, for example, may show disruptive behaviour because of their inability to express themselves sufficiently. Another hypothesis is that developmental and behavioural problems have common grounds, such as particular brain network aberrations that may arise in early neurodevelopment.[39]

Little is known on the subject of co-occurrence of developmental and behavioural problems in preterm-born children. A few studies have shown higher rates of co-occurring problems in very preterm-born children.[40, 41] Up to half of the preterm-born children appeared to have more than one developmental or behavioural disability at the age of five years, compared to 8% in full-term children.[40, 41] As yet, in MP children, however, the prevalence of co-occurring developmental and behavioural problems is unknown. Furthermore, to the best of our knowledge, MP children have not been compared with full-term children regarding co-occurrence. If a trend towards increasing co-occurrence rates with decreasing gestational age were to be found, this could provide clues for the underlying mechanisms of co-occurring problems. In the case of MP children, the lack of three to eight weeks of intrauterine brain growth might increase the likelihood of the type of brain network aberrations suggested in the literature.

Influence of socioeconomic status on neurodevelopmental problems

Low family SES is strongly associated with developmental and behavioural and emotional problems.[24, 42] One important pathway explaining this association is the higher prevalence of stress-inducing situations in socioeconomically disadvantaged families.[43, 44] Experiences of early life adversities show a clear dose-response relationship with cardiovascular and mental health problems throughout life.[43, 45, 46] Low SES and associated circumstances may even cause permanent changes in brain functions and body regulation systems, affecting the foundations of mental and physical health.[47, 48]

Is low SES an explanation for worse neurodevelopmental outcomes in MP children?

The effects of moderate prematurity on developmental, behavioural, and social-emotional problems may be different in children from low SES families.[49] First of all, preterm delivery is more likely to occur in mothers with low SES.[50-52] In

socioeconomically deprived areas up to 12% of deliveries are preterm, compared to 3% to 7% in prosperous areas.[53] One of the explanations for this difference is that many risk factors for preterm delivery are socioeconomically graded, such as obesity, hypertension, smoking, psychological stress, and inadequate use of prenatal care.[50, 52, 54]

As mentioned previously, children from low SES families are more likely to be exposed to early adversities than children from high SES families. Early adversities have been linked with altered functioning of several brain areas and body regulation systems [55, 56] and with lower psychological well-being of parents, which affects parent-child interactions.[57, 58] Anyhow, low family SES increases the likelihood of developmental and behavioural problems in offspring, and this may, at least partly, explain why MP children are at greater risk of neurodevelopmental problems than full-term children.

How to measure SES?

SES is defined as "an individual's or group's position within a hierarchical social structure".[59] Several indicators have been used to measure SES, and they all refer to societal stratification in a slightly different way. Education, occupation, and income are the SES indicators that are most frequently used in health research.[60, 61] The level of education reflects cognitive capacity, opportunities for education, parents' education and its influence on their children, and the resources available to the family.[60] Occupation is related to social standing, the ability to build up networks, the degree of work-related stress, autonomy, and job-related, exposure to toxic substances.[60] Higher occupational class does not necessarily stand for better health conditions. Effects of work-related stress may, for example, be greater in higher than in lower occupations. Income reflects material resources which could mean easier access to social and medical services, more self-esteem and social standing, and it allows consumption of health-promoting commodities.[60] Because of the interrelationships between different SES indicators, composite SES measures of these indicators provide investigators with the opportunity to fully account for the effects that can be attributed to socioeconomic conditions.[60, 62]

A life course perspective on neurodevelopment

Potentially, disruptions of neurodevelopment in the prenatal period and early postnatal years have lifelong effects on health.[63-65] Evidence is accumulating that early adverse events and environments, such as maternal stress during pregnancy

and socioeconomic disadvantage early in life, lead to neurodevelopmental disorders in childhood and psychiatric and cardiovascular disorders in adulthood.[43, 45, 46, 66-68] Nevertheless, much still needs to be unravelled regarding underlying disease mechanisms.[69, 70] Below, we begin by providing a brief summary of the literature on the developmental origins of health and disease followed by a description of what is known on the subject of healthy emotional functioning in childhood in relation to coronary heart disease (CHD).

Developmental Origins of Health and Disease (DOHaD)

The DOHaD concept has its roots in the Barker Hypothesis. In the 1980s and early 1990s, Barker and his colleagues discovered the link between low birth weight, which reflects impaired foetal growth, and CHD. Later, this was referred to as the Barker Hypothesis.[68, 71] According to Barker, the link could be regarded as a 'manifestation of developmental plasticity', which he described as 'a critical period when a system is plastic and sensitive to the environment, followed by loss of plasticity and fixed functional capacity'.[68] In other words, the rapid neurodevelopmental processes that take place in foetal life and early childhood,[1] may function to provide a human being with opportunities to adapt to the demands posed by the environment.

In recent decades, many indicators of early environmental adversity have been incorporated in the DOHaD concept, including malnutrition and exposure to infection and stress,[72-74] and knowledge on this topic is still expanding. As such, various early stressful experiences have been associated directly with altered functioning of several areas of the brain and regulation systems of the body, for example, those involving the hypothalamic-pituitary-adrenal axis circuitry.[55, 56, 69, 75] Combined with clinical and epidemiological research, these findings provide further clues for underlying mechanisms explaining the links between early adverse environments, neurodevelopmental problems, affective disorders, and coronary heart disease.[69, 76]

Affective disorders, childhood emotional functioning, and the risk of CHD

During the past sixty years, in their endeavour to understand the aetiology of CHD, investigators have become increasingly interested in psychosocial factors.[46] Psychosocial risk factors for CHD can be broadly subdivided into affective disorders (anxiety/depression), personality features, and chronic psychological stress, either work-related or private. The strongest evidence was found for the association between

affective disorders and CHD. The underlying mechanisms for causal associations between psychosocial factors and CHD are gradually becoming clearer. Mainly two pathways were suggested: 1) an indirect mechanism via the effect of psychosocial factors on lifestyle-associated risk factors for CHD, such as body mass index and smoking, and 2) a direct mechanism via the adverse effects of psychological stress on body regulation systems that affect cardiovascular reactivity.[77, 78]

Affective disorders and CHD may have common origins in foetal development and early childhood given the high co-occurrence of depression and CHD.[69] Nevertheless, as mentioned earlier, many disease mechanisms are yet to be unravelled. This also applies to the pathways between early neurodevelopmental disruptions, depression, and CHD many years later. Recently, associations between several indicators of poor childhood emotional functioning and CHD precursors were investigated.[79, 80] Emotional functioning has its roots in early childhood,[81, 82] and may be a plausible explanation for developmental origins of affective disorders and CHD.[80, 83] More specifically, deficits in emotion regulation, one dimension of emotional functioning, may play a role in the onset of depressive disorders,[83] but it has not yet been associated with CHD. Refinement of this hypothesis may offer opportunities for clinical and prevention purposes that are potentially beneficial to many individuals, including preterm-born and low SES children.[84, 85]

OUTLINE OF THE THESIS

The overall aim of the studies presented in this thesis was to determine the associations between moderate prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective. The specific research questions were:

1. Are moderate prematurity and low SES independently associated with developmental delay at pre-school age, or do they have joint effects? (**Chapter 2**)
2. What is the prevalence of behavioural and emotional problems in four-year-old, moderately preterm-born children, compared to the prevalence in full-term children? (**Chapter 3**)
3. Are moderate prematurity and low SES independently associated with behavioural and emotional problems at pre-school age, or do they have joint effects? (**Chapter 4**)

4. What is the prevalence of developmental delay co-occurring with behavioural and emotional problems in four-year-old, moderately preterm-born children compared to the prevalence in full-term controls? (**Chapter 5**)
5. Does poor emotion regulation in 18-year-olds predict the risk of coronary heart disease? (**Chapter 6**)

In order to answer the first four research questions (Chapters 2 to 5), we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP), a Dutch prospective cohort study. It was designed to investigate growth, development, and general health of preterm-born children, with a special focus on those children who were born moderately preterm. The participants were recruited from thirteen preventive child healthcare (PCH) centres during 2006 and 2007. In the Netherlands, the development of children is closely monitored by PCH centres from birth up to four years of age. This service, which is free, is offered actively and systematically to all Dutch families and reaches 95% to 97% of the Dutch child population. More details on the sampling procedures are displayed in the flow chart in Appendix 1.

In Chapter 2, we determine the influence of SES on developmental delay in MP children and full-term children. This is followed in Chapters 3 and 4, by our comparison of MP and full-term children regarding behavioural and emotional problems at preschool age, overall and by gender. Chapter 4 focuses on the effect of SES on behavioural and emotional problems in MP children. Next, in Chapter 5, we report on our investigation of the co-occurrence of developmental and behavioural problems in MP and full-term children at the age of four years. The Ages and Stages Questionnaire (ASQ) and CBCL were used to assess developmental and behavioural outcomes. The ASQ is a parent-completed screening instrument[86] that has been validated for many countries, including the Netherlands.[87] It measures development in five developmental domains: fine motor, gross motor, communication, problem solving, and personal-social. The CBCL is also a parental questionnaire that is widely used in various clinical settings and in research.[88] Scores on CBCL items can be added up to provide a score for internalizing and externalizing problems. To serve as an example, the Dutch versions of the ASQ and CBCL that were used in the LOLLIPOP study are included in Appendices 2 and 3, respectively.

In Chapter 6, we describe the role of young individuals' emotional functioning for lifelong health. We investigated the association between one dimension of

emotional functioning, i.e. emotion regulation, and the long-term risk of heart disease. For this study, we used data from a nationwide survey of Swedish males who were conscripted for compulsory military service in 1969 and 1970. The procedures and variables of this study were described elsewhere.[89, 90]

Finally, in Chapter 7, which comprises the General discussion, we provide an overview of the main findings and discuss these in the light of the relevant literature. This chapter ends with several implications for clinical practice, policy, and research. Chapter 8 contains the English and Dutch summaries of the research presented in this thesis.

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Chapter 2

Developmental delay in moderately preterm-born children with low socioeconomic status: risks multiply

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ABSTRACT

Objective Socioeconomic status (SES) may (partially) explain associations of moderate prematurity with developmental delay. Therefore, we assessed separate and joint effects of low SES and moderate prematurity on preschool developmental delay.

Study design Prospective cohort study with a community-based sample of preterm- and term-born children (Lollipop-study). We assessed SES on the basis of education, occupation, and family income. The Ages and Stages Questionnaire was used to assess developmental delay at age four. We determined scores for overall development, and domains fine motor, gross motor, communication, problem-solving, and personal-social of 926 moderately preterm-born (32-36 weeks' gestation) and 544 term-born children. In multivariable logistic regression analyses, we used standardized values for SES and gestational age (GA).

Results Prevalence rates for overall developmental delay were 12.5%, 7.8%, and 5.6% in moderately preterm-born children with low, intermediate, and high SES, respectively, and 7.2%, 4.0%, and 2.8% in term-born children, respectively. The risk for overall developmental delay increased more with decreasing SES than with decreasing GA, but the difference was not statistically significant: odds ratios (95% confidence intervals) for a one standard deviation decrease were: 1.62 (1.30-2.03) and 1.34 (1.05-1.69), respectively, after adjustment for gender, number of siblings, and maternal age. No interaction was found except for communication, showing that effects of SES and GA are mostly multiplicative.

Conclusions Low SES and moderate prematurity are separate risk factors with multiplicative effects on developmental delay. The double jeopardy of moderately preterm-born children with low SES needs special attention in pediatric care.

INTRODUCTION

Worldwide, one in ten live births ends before 37 weeks of gestational age (GA).[1] Although children born at less than 32 weeks of gestation face the greatest risk of mortality and morbidity, more than 85% of preterm children are born beyond 32 weeks' of gestation.[2] Every week, therefore, that a child is born closer to term, decreases the risk of mortality and morbidity,[3] but it increases the impact on public health due to the much larger number of children involved.[4]

In the long-term, moderately preterm-born children (MP; 32 to 36 weeks' gestation) face significantly more developmental problems than term-born children (38 to 42 weeks' gestation).[5-8] In MP children aged four, the risk of developmental delay is twice the risk of term-born children and half the risk of very preterm children (< 32 weeks' gestation).[6] Huddy et al. reported that up to one third of MP children will have difficulties functioning at school.[7] Specifically fine motor skills and handwriting seem to be affected.[6,7-9]

Recent evidence indicated that differences in socioeconomic status (SES) may (partially) explain the association of moderate prematurity with developmental delay.[5,10] Additionally, low SES may further increase the effects of moderate prematurity on development. Nevertheless, the role of SES in the relationship between moderate prematurity and developmental delay is unclear. Our aim was, therefore, to assess the separate and joint effects of moderate prematurity and low SES on developmental delay in early childhood.

METHODS

Study design

Data used for this study are from the Longitudinal Preterm Outcome Project (Lollipop): a large prospective cohort study, designed to investigate growth, development, and general health of preterm-born children, with a special focus on MP children (32^0 to 35^6 weeks of gestation) in the Netherlands.[6] Lollipop consists of a community-based sample of preterm children and a random sample of term-born controls (38^0 to 41^6 weeks of gestation). At the stage in which the study was designed, MP children concerned those children born at 32-35 weeks gestation and therefore children born at 36^0-36^6 weeks gestation were not included. Participants were recruited from thirteen randomly selected Preventive

Child Health Care (PCH) centers from across the country, covering urban and rural areas. Together, the thirteen centers monitored 45 446 children (25% of all four-year-old children monitored by Dutch PCH centers). In the Netherlands, 90% to 95% of children are seen regularly and free of charge by PCH doctors of well-child care from birth up to four years.[11] PCH professionals monitor mental and physical development through structured interviews with parents, general physical examinations, and standardized screening procedures, all of which are documented in PCH files. Lollipop was approved by the local institutional review board, and written informed consent was obtained from all parents. Lollipop is registered with www.controlled-trials.com (ISRCTN 80622320).

Participants

Each PCH center provided a sample of all preterm children born during a single year, either from January 2002 to January 2003 or from June 2002 to June 2003. Term-born children were sampled from the same PCH centers and belonged to the same age-range as the preterm children. After the file of each second preterm child had been selected, the file of the next term-born child served as a control. In >95% of cases, GA was calculated by using the last date of menstruation, and confirmed by early ultrasound measurements. In the Netherlands, it is routine practice to assess GA with early ultrasound measurements between 10^0 and 12^6 weeks of gestation. Children were excluded if they had a congenital malformation or syndrome, if the GA could not be verified or was beyond the set range, or if families moved between sampling and inclusion. An overview of the sampling procedures of Lollipop has previously been provided by Kerstjens et al.[6] In short, of the 1145 eligible MP children, 995 (86.9%) parents participated in the long-term follow-up part of the study and of the 674 eligible term-born children, 577 (85.6%) parents participated. Response rates for the developmental questionnaire were 81.0% for MP children and 80.7% for term-born children. The total number of children in this study is 1470 (926 MP and 544 term-born children).

Assessment of SES

We determined SES on the basis of the three most frequently used measures: education, income, and occupation.[12,13] Data on the highest completed educational level of both parents were collected by a questionnaire when the children were four years old. The following categories were defined: primary school or less, low-level technical and vocational training (< 12 years of education), high school or medium-

level technical and vocational training (12 to 16 years of education), and university or high-level technical and vocational training (> 16 years of education). Furthermore, parents were asked to give an indication of their net monthly household income in euros: ≤ €850 ($1,087), €851 to €1150 ($1,088 to $1,471), €1151 to €1750 ($1,472 to $2,239), €1751 to €3050 ($2,240 to $3,902), €3051 to €3500 ($3,903 to $4,477), and > €3500 ($4,477). Data on occupational level were collected retrospectively from medical records kept by the PCH centers. We classified the occupational level of both parents according to the International Standard Classification of Occupations.[14] We assessed the composite SES score on the basis of five indicators: educational level of father, educational level of mother, family income, occupational level of father, and occupational level of mother. Information on each of the five indicators was available for 95%, 98%, 76%, 81%, and 71%, respectively, of the children participating in this study. We standardized each of the indicators and computed the mean per child of the indicators that were available for that child, resulting in one single SES score for each child. Then the SES scores were again standardized, i.e. had a mean of 0 and an standard deviation of 1.

Developmental outcomes

Developmental outcomes were measured using the Dutch version of the 48-month form of the Ages and Stages Questionnaire (ASQ), which is a validated, parent-completed, developmental screening instrument.[15,16] We computed five developmental domains of the ASQ: fine motor, gross motor, communication, problem-solving, and personal-social skills.[16] Each domain consists of six questions on developmental milestones. For example, the domain communication problems consists of questions about the notion of categories, interpretation, meaning of objects, word conjugations, operating instructions, and the ability to form full sentences. Parents were asked to evaluate whether their child had achieved a milestone (yes, ten points), had partly achieved a milestone (sometimes, five points), or had not yet achieved a milestone (no, zero points). Furthermore, we computed the ASQ total score by taking the mean of the five domain scores. For the total score and the domains scores cut-offs for normal and abnormal scores were set at two standard deviations below the mean score of the Dutch reference group.[15] In > 95% of cases, the mother filled out the questionnaire.

Statistical analyses

Firstly, we assessed child and family characteristics across children with low, intermediate, and high SES. Secondly, we examined prevalence rates of ASQ scores in the abnormal range for term-born and MP children with low, intermediate, and high SES. Thirdly, we performed univariate logistic regression analyses to assess the crude effect of SES and GA on developmental delay by using standardized scores for SES and GA, meaning that both have a mean of 0 and standard deviation of 1. Finally, we assessed the effects of SES, GA, and the interaction between SES and GA on developmental delay in three consecutive multivariable logistic regression models. In the first model we assessed separate effects of SES and GA, with mutual adjustment. Next, we assessed potentially synergistic effects of SES and GA by adding the SES*GA interaction (Model 2). In the final Model 3 we adjusted for the effect of potential confounders, which were identified on the basis of the literature and differences in background characteristics. We decided not to adjust for family composition and ethnicity of the mother to prevent over-adjustment for factors that significantly correlated with SES. We used SPSS for Windows 18.0 for all the statistical analyses. A *P* value of less than .05 was considered statistically significant.

RESULTS

In *Table 1* we show the characteristics of all preterm and term children with low, intermediate, and high SES. Characteristics were statistically different between SES groups for family composition, maternal age, and maternal ethnicity. In analyses for the preterm and term-born children separately, we found no other characteristics that differed with statistical significance. The GA distribution of the 926 MP children was: 32 weeks, 113 (12.2%); 33 weeks, 177 (19.1%); 34 weeks, 257 (27.8%); 35 weeks, 379 (40.9%).

Figure 1 shows prevalence rates of ASQ scores in the abnormal range for term-born children **(A)** and MP children **(B)** with low, intermediate, and high SES. Except for domains gross motor and communication (MP children), the proportion of children with scores in the abnormal range increased as SES decreased. For the ASQ total score, prevalence rates were 7.2%, 4.0%, and 2.8% in term-born children with low, intermediate, and high SES, respectively, compared to 12.5%, 7.8%, and 5.6% in MP children, respectively.

Table 1 Characteristics of moderately preterm-born and term-born children with low, intermediate, and high socioeconomic status[a] (n=1470)

Variable	**Low** N=260	**Intermediate** N=937	**High** N=273	*P* value[b]
	% (n)	*% (n)*	*% (n)*	
Moderately preterm-born	71.9 (187/260)	61.5 (576/937)	59.7 (163/273)	.004
SGA (<P10)[c]	10.4 (27/260)	8.3 (78/937)	9.2 (25/273)	.57
Male gender	58.5 (152/260)	53.8 (504/937)	53.1 (145/273)	.36
Age of child[d]				.77
45-51 months (%)	60.4 (148/245)	62.7 (572/912)	63.2 (170/269)	
Mean (SD)	45.0 (1.3)	45.1 (1.4)	45.1 (1.3)	
Family composition				
Two-parent family	87.9 (226/257)	94.8 (886/935)	98.5 (269/273)	< .001
One-parent family	12.1 (31/257)	5.2 (49/935)	1.5 (4/273)	
Number of siblings				
0	19.6 (51/260)	16.6 (156/937)	13.2 (36/273)	.07
1	50.0 (130/260)	55.7 (522/937)	57.9 (158/273)	
2	19.6 (51/260)	21.5 (201/937)	22.3 (61/273)	
≥ 3	10.8 (28/260)	6.2 (58/937)	6.6 (18/273)	
Age mother				
< 25	13.6 (35/258)	7.8 (73/935)	1.1 (3/273)	< .001
25 to 34	68.2 (176/258)	74.0 (692/935)	72.9 (199/273)	
> 34	18.2 (47/258)	18.2 (170/935)	26.0 (71/273)	
Ethnicity of mother				
Netherlands	90.3 (232/257)	95.3 (886/930)	96.3 (261/271)	< .001
Europe	0.4 (1/257)	1.8 (17/930)	2.2 (6/271)	
Outside of Europe	9.3 (24/257)	2.9 (27/930)	1.5 (4/271)	
Education of mother[e]				< .001
Low	7.8 (20/258)	0.5 (5/933)	-	
Low to intermediate	82.9 (214/258)	19.0 (177/933)	-	
Intermediate to high	9.3 (24/258)	61.5 (574/933)	13.6 (37/272)	
High	-	19.0 (177/933)	86.4 (235/272)	
Education father[e]				< .001
Low	11.4 (26/228)	1.2 (11/917)	-	
Low to intermediate	78.9 (180/228)	26.9 (247/917)	0.4 (1/272)	
Intermediate to high	9.6 (22/228)	50.6 (464/917)	8.1 (22/272)	
High	-	21.3 (195/917)	91.5 (249/272)	
Family income (euro)[e]				< .001
< 850	4.3 (8/186)	0.6 (4/722)	-	
851-1150	24.7 (46/186)	3.2 (23/722)	-	
1151-1750	43.0 (80/186)	15.9 (109/722)	0.9 (2/229)	
1751-3050	28.0 (52/186)	69.1 (499/722)	27.9 (64/229)	
3051-3500	-	8.6 (62/722)	24.5 (56/229)	
>= 3501	-	3.5 (25/722)	46.7 (107/229)	

[a] Low SES, scores <= mean -1 SD on standardized SES scale; intermediate SES, scores > mean -1SD and <= mean +1SD; high SES, scores > mean +1 SD.

[b] *P* values are based on chi-squared tests.

[c] SGA, small for gestational age; i.e. birth weight below the 10th percentile of the Dutch Kloosterman growth charts.

[d] Age at completing the Ages and Stages Questionnaire; uncorrected calendar age. The percentages of children with an age that is appropriate for the 48-month version of the ASQ are given (i.e. between 45 and 51 months of age).

[e] Extensive information on SES indicators is defined in the Methods section.

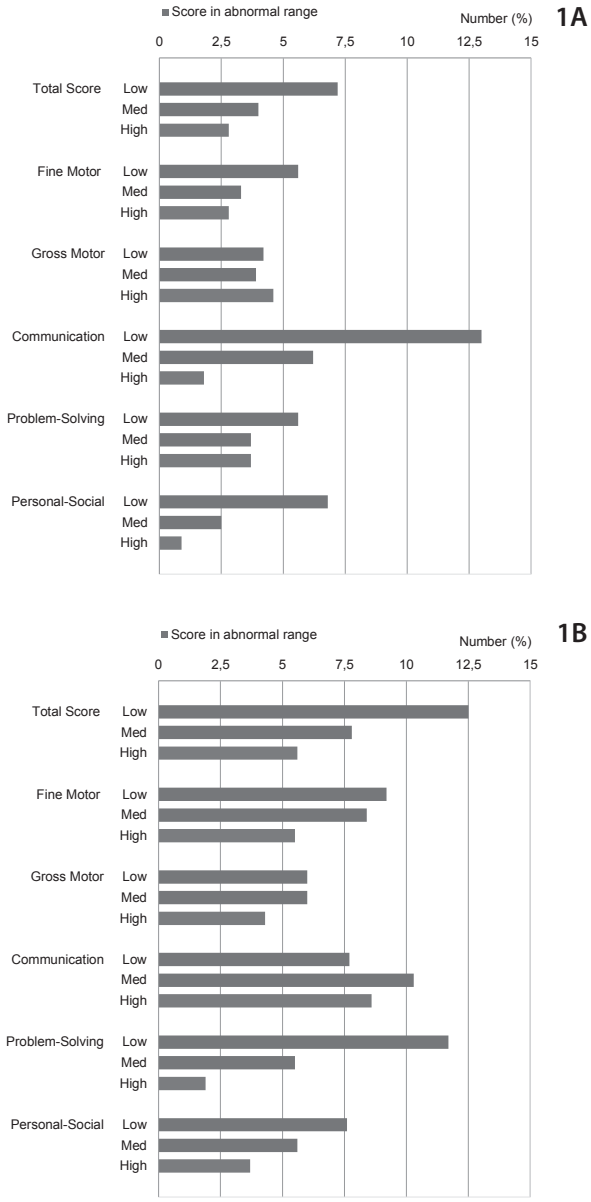

Figure 1 Scores in the abnormal range on the Ages and Stages Questionnaire (ASQ) for children of low, intermediate, and high socioeconomic backgrounds. For ASQ total development and the five ASQ domains, scores were called 'abnormal' at two standard deviations or less below the mean score of the Dutch reference group. **1A**, Scores on the ASQ by SES in term-born children (n = 544). **1B**, Scores on the ASQ by SES in MP children (n = 926).

Information on the percentage of children having abnormal ASQ scores is given in *Table 2*, for all children together, and for low SES and MP children separately. Of the 1470 participating children 6.8% had a total development score two standard deviations below the mean of the Dutch reference group. For low SES and MP children these percentages were 11.0% and 8.3%, respectively.

Table 2 Overview of abnormal scores on the Ages and Stages Questionnairea for all children together, and for low SES and moderately preterm-born children separately

	All children	**Low SES**[b]	**Moderately preterm**
ASQ Domains	*n=1470* % (*n*)	*n=260* % (n)	*n=926* % (n)
Total Score	6.8 (96/1416)	11.0 (27/245)	8.3 (74/891)
Fine Motor	6.4 (93/1458)	8.2 (21/256)	8.1 (74/917)
Gross Motor	5.1 (74/1450)	5.5 (14/256)	5.7 (52/911)
Communication	8.3 (119/1436)	9.2 (23/251)	9.5 (86/906)
Problem-Solving	5.3 (76/1444)	10.0 (25/251)	6.1 (55/908)
Personal-Social	4.6 (67/1455)	7.4 (19/257)	5.7 (52/915)

Abbreviations: SES, socioeconomic status; ASQ, Ages and Stages Questionnaire

[a] Abnormal score on the ASQ: scores two standard deviations or more below the mean score of the Dutch reference group.

[b] Low SES: one standard deviation or more below the mean of the standardized SES.

In *Table 3* we present three models of multivariate logistic regression analyses, using standardized values for SES and GA. The highest values of SES and GA served as reference. Odds ratios represent the effect of a one standard deviation decrease in SES or GA. In multivariate Model 1, we assessed separate effects of SES and GA, with mutual adjustment. Decreasing SES was associated with an increased risk of delay in overall development, fine motor, communication, problem-solving, and personal-social skills. Decreasing GA was associated with an increased risk of delay in overall development, fine motor and communication skills. In Model 2 we analyzed synergistic effects of SES and GA (SES*GA). No statistically significant interaction effects were found, except for communication skills. This indicates that the joint effects of SES and GA on communication skills are less than multiplicative. For the other domains and for overall developmental delay, the effects of SES and GA are multiplicative, as is the case for any logistic model without interactions. In the final and adjusted Model, decreasing SES and decreasing GA were both associated with an increased risk of delay in overall development and delay in the domains fine motor, communication, and personal-social. Only decreasing SES significantly increased the risk of problem-solving skills. Lastly, we found no relationship of decreasing SES or GA with delay in gross motor skills.

Table 3 Relative and joint effects of socioeconomic status and gestational age on developmental delay: results of three multivariate logistic regression models

	Univariate	**Model 1**[a]	**Model 2**[b]	**Model 3**[c]
ASQ Domains	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total Score				
Decreasing SES[d]	**1.70 (1.37-2.11)*****	**1.67 (1.34-2.07)*****	**1.67 (1.27-2.20)*****	**1.62 (1.30-2.03)*****
Decreasing GA[e]	**1.36 (1.09-1.71)****	**1.32 (1.05-1.65)***	1.32 (0.96-1.81)	**1.34 (1.05-1.69)***
SES*GA			0.99 (0.71-1.40)	
Fine Motor				
Decreasing SES[d]	**1.31 (1.06-1.62)***	**1.28 (1.03-1.58)***	1.24 (0.92-1.67)	**1.30 (1.05-1.62)***
Decreasing GA[e]	**1.49 (1.18-1.89)*****	**1.47 (1.16-1.86)*****	**1.42 (1.05-1.93)***	**1.44 (1.13-1.85)*****
SES*GA			1.06 (0.73-1.53)	
Gross Motor				
Decreasing SES[d]	1.09 (0.86-1.37)	1.07 (0.85-1.36)	1.01 (0.74-1.40)	1.09 (0.86-1.38)
Decreasing GA[e]	1.16 (0.91-1.48)	1.16 (0.91-1.47)	1.10 (0.80-1.50)	1.14 (0.89-1.46)
SES*GA			1.12 (0.74-1.68)	
Communication				
Decreasing SES[d]	**1.37 (1.13-1.65)*****	**1.34 (1.11-1.62)*****	**1.57 (1.24-1.98)*****	**1.50 (1.18-1.90)*****
Decreasing GA[e]	**1.30 (1.07-1.59)****	**1.27 (1.04-1.56)***	**1.53 (1.18-2.00)*****	**1.60 (1.22-2.10)*****
SES*GA			**0.73 (0.55-0.97)***	**0.73 (0.55-0.98)***
Problem-Solving				
Decreasing SES[d]	**1.85 (1.44-2.36)*****	**1.82 (1.42 to 2.33)*****	**1.76 (1.30-2.37)*****	**1.79 (1.39-2.30)*****
Decreasing GA[e]	**1.30 (1.02-1.66)***	1.24 (0.97 to 1.60)	1.18 (0.82-1.69)	1.29 (1.00-1.66)
SES*GA			1.09 (0.75-1.58)	
Personal-Social				
Decreasing SES[d]	**1.49 (1.16-1.92)*****	**1.47 (1.14-1.88)*****	**1.58 (1.16-2.14)*****	**1.33 (1.03-1.72)***
Decreasing GA[e]	**1.34 (1.02-1.74)***	1.30 (0.99-1.69)	1.43 (1.00-2.05)	**1.36 (1.03-1.80)***
SES*GA			0.86 (0.59-1.25)	

[a] Model 1: assessing the effects of socioeconomic status (SES) and decreasing gestational age (GA) in a multivariate model.

[b] Model 2: assessing potentially synergistic effects of SES and GA, by adding the SES*GA interaction to Model 1.

[c] Model 3: adjusting Model 1 (Model 2 for communication problems) for gender, number of siblings, and maternal age.

[d] Decreasing SES: the odds ratio (OR) represents the effect of every standard deviation (SD) decrease in SES with respect to the highest SES value (reference). On the standardized SES scale 260 children had a SES score < 1 SD below the mean (low SES), of which 6 children (2.3%) had a SES score < 2 SD below the mean.

[e] Decreasing GA: the OR represents the effect of a one SD (i.e. ~ 3 weeks) decrease in GA compared to the highest GA value. Mean GA was 36 weeks.

Levels of significance: * indicates $P < .05$, ** indicates $P < .01$, and *** indicates $P < .005$

DISCUSSION

Our study showed that moderate prematurity and low SES are separate risk factors with multiplicative effects on developmental delay in early childhood. Only effects on communication skills were less than multiplicative. Decreasing SES and decreasing GA were both associated with increased risks of delay in overall development and delay in domains fine motor, communication, and personal-

social skills. The risk of delay in problem-solving skills was significantly associated with decreasing SES but not with decreasing GA.

Our finding that moderate prematurity and low SES were separate risk factors for developmental delay supports the findings of two recent studies. A study of Woythaler et al. showed that medical factors, including moderate preterm birth at 34 to 37 weeks' gestation, as well as sociodemographic factors affected neurodevelopmental outcomes at 24 months of age.[5] Quigley et al. reported that both moderate prematurity and low maternal educational level were associated with poorer educational achievement at age five.[10] Furthermore, in these studies socioeconomic factors had a greater share in poor developmental or educational outcomes than GA. This seems to be the case in our study too, though mainly for problem-solving skills.

Because of the higher rate of prematurity among low SES families, the association of moderate prematurity with developmental delay could have been a reflection of low SES effects. This was hypothesized while many socioeconomically-graded risk factors have been identified for preterm delivery, such as obesity, hypertension, smoking and stress. However, we found that SES neither weakened nor strengthened the association between moderate prematurity and developmental delay. Therefore, our results support the hypothesis that GA itself is linked to developmental delay.

Developmental problems are rather common in early preterm-born children, as reported in several studies.[6,17-19] The risk increases with decreasing GA: it has been suggested that e.g. intelligence quotient decreases 1.7 to 2.5 points per week below 32 weeks of gestation.[19] MP children miss out on four to eight weeks of brain growth and development in utero, which may also put them at risk of developmental problems. Moderate prematurity has been associated with a smaller, and more specific array of developmental problems than early prematurity. Impairments include impaired fine motor skills, handwriting, coordination, and verbal fluency.[6,7,9,10] Higher rates of white matter injury in early preterm-born children explain a part of this difference, but the developmental stage of the central nervous system at birth might be even more important.[17,20] Evidence from neuroscience shows that microstructural and neural connectivity processes are disturbed due to prematurity and this disturbance may result in atypical differentiation of neuronal pathways.[21] Especially the limbic system and the cerebellum undergo structural changes after 32 weeks of gestation, and missing four to eight weeks of brain growth and development in utero may manifest itself later in difficulties

controlling complex motor or mental tasks.[17,22-23] We believe that our findings on the effects of decreasing GA in moderate prematurity are mainly explained by these observations, but this is speculative. Other determinants involved in the long-term development of preterm children are for example maternal health in pregnancy and the reason for the preterm delivery.

We found that SES and GA had multiplicative effects on delays in overall development, fine motor, and personal-social skills, which means a double jeopardy for MP children with low family SES. The significant interaction for communication shows that SES and GA had no multiplicative effects on communication skills. Each of the risk factors independently increased the risk of delay in communication skills, but the joint effect of having both risk factors was hardly greater than the effect of having only one risk factor. Although effects were not multiplicative, SES and GA did have a strengthening influence on each other's independent effect (greater after adding the interaction). We presume that other factors may be involved here which are linked to low SES and/or moderate prematurity and which are associated with a higher risk of delay in communication skills. MP children could for example be offered more special care services than term-born children, which may have improved the communication skills of MP children. However, against this explanation pleads that MP children have just recently been recognized as a high-risk group.[24] Apparently, this issue requires additional study.

Decreasing SES was associated with an increased risk of delay in all domains except gross motor skills. Low SES is found to be associated with language processing and executive functioning[25], and this may explain the relationship of low SES with almost all ASQ domains. Furthermore, numerous potential mediators can be named which contribute to the effect of low SES on delays in language processing and executive functioning. The broadest support, however, was found for prenatal factors, parental involvement and care, and cognitive stimulation in the home environment.[25]

Our study had several strengths as well as limitations. An important strength was the large community-based sample, which was well-suited to examine the effects of both moderate prematurity and SES. Furthermore, response rates were high on the developmental questionnaire: more than 90% of parents returned the questionnaires. Finally, SES was measured very accurately and comprised three of the most frequently used measures, i.e. occupation, education, and income.[12]

One limitation of our study was that we used a parent-completed screening instrument for the measurement of developmental delay instead of professional testing. However, the ASQ is a reliable and valid questionnaire for developmental screening.[15,16,26] We notice that not all ASQ scores were complete. Some parents may have had challenges in comprehending the questions, for example mothers in the low SES group having an 'ethnicity outside Europe'. In general, however, parents consider the ASQ easy to fill out,[27] and most parents (97%) can do so without the help of others.[28] Another limitation was that our study lacked information on factors that may explain some of the effects of SES such as genetic factors.

Our findings have two main implications. Firstly, we found that low SES and moderate prematurity are separately associated with developmental delay, and thus their effects multiply each other. Therefore, in PCH trajectories more attention should be paid to the double jeopardy of the large group of MP children with low SES. Secondly, preventive actions and/or early intervention may prevent (further) developmental delay in these high-risk children. One possible strategy to prevent developmental delay in both poor children and in preterm infants may be home-visiting of nurses at an early stage.[29] However, before starting new preventive programs, further investigation is needed on the effectiveness of early intervention in MP children. In addition, modifiable mechanisms need to be identified that link low SES to adverse developmental outcomes.[25,30, 31]

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Chapter 3

Higher rates of behavioural and emotional problems at preschool age in children born moderately preterm

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ABSTRACT

Objective To compare pre-school moderately preterm-born (MP; 32-35 weeks' gestation) and term-born (38-41 weeks' gestation) children regarding the occurrence of behavioural and emotional problems, overall, for separate types of problems, and by gender.

Design Prospective cohort study consisting of a community-based sample of MP and a random sample of term-born children.

Setting Thirteen Preventive Child Health Care centres throughout the Netherlands.

Patients We included 995 MP and 577 term-born children, just under age four.

Main outcome measures Behavioural and emotional problems were measured using the Child Behavior Checklist (CBCL) 1.5-5 years. Seven syndrome scales, and internalizing, externalizing, and total problems were determined. Higher scores indicate a worse outcome.

Results MP children had higher scores on all syndrome scales, internalizing, externalizing, and total problems than term-born controls. The mean difference on total problems was 4.04 (95% confidence interval [CI] 2.08-6.00). Prevalence rates of elevated externalizing problem scores were highest in boys (10.5%) and internalizing problems were highest in girls (9.9%). MP children were at greater risk for somatic complaints (odds ratio [OR], 95% CI: 1.92, 1.09-3.38), internalizing (OR 2.40, 95% CI 1.48-3.87), externalizing, (OR 1.69, 95% CI 1.07-2.67), and total problems (OR 1.84, 95% CI 1.12-3.00).

Conclusions Moderate preterm birth affects all domains of behavioural and emotional problems, particularly for girls. MP children could be a potential target group for the prevention of mental health problems, because these problems have a great impact on the developmental and social competencies at school and in the community.

What is already known on this topic

- ▷ Children born moderately preterm are at increased risk for neonatal mortality and for short- and long-term health problems.
- ▷ It has been suggested that moderate preterms may also be at risk for separate types of behavioural and emotional problems.
- ▷ However, large prospective cohort studies are lacking.

What this study adds

- ▷ The occurrence of behavioural and emotional problems was higher in moderate preterm-born children than in term-born controls, overall and for separate types of problems.
- ▷ In both groups the prevalence of behavioural and emotional problems was higher among boys, but being a moderate preterm affected girls more than boys.

INTRODUCTION

Worldwide the preterm birth rate in 2005 was an estimated 9.6% (12.9 million births).[1] The highest rates were in Africa (11.9%) and North America (10.6%) and the lowest rates in Europe (6.2%).[1] In the Netherlands 7.7% of children were born preterm in 2008.[2] United States data show a rise in the preterm birth rate from 9.4% in 1981 to 12.3% in 2003, with the highest increase in rates of moderately preterm-born children (MP; 32-35 weeks' gestation).[3] The rate of children born very preterm (<32 weeks) remained relatively constant during the same period at 1.8 to 2.0%. In other words, children born after 32 weeks gestation comprise more than 85% of all preterm births.[3-5]

Accumulating evidence shows that MP children are at greater risk for developmental and health problems than term-born children (38-41 weeks' gestation). Several follow-up studies have reported that MP children are not only at risk for short-term morbidity and mortality,[6-8] but also for numerous developmental and school-related problems in the long-term.[9-11]

However, evidence concerning long-term behavioural and emotional problems among MP children is limited.[12-16] One study on 52 late preterm-born children (born at 34-36 weeks) showed no differences in externalizing, internalizing, aggressive, and anxious/depressed problems compared to term-born children.[12] In contrast, Van Baar et al. reported that MP children were more likely to have behavioural and emotional problems at ages 7 to 9, specifically attention and internalizing problems.[13] A recent study of Talge et al. confirmed the presence of more attention and internalizing problems in 6-year-old children born at 34-36 weeks' gestation.[14] Furthermore, Gray et al. reported that ~20% of MP children with low birth weight had behavioural problems at 3, 5 and 8 years of age, compared to the expected 10% in normative samples if using the same cut-off.[15, 17]

Although it is shown that very preterm and low birth weight children have considerably more behavioural and emotional problems,[18] large prospective cohort studies on moderately and late preterm-born children are lacking. The few small studies showed conflicting results.[12-14] Therefore, the purpose of this study was to determine the occurrence of behavioural and emotional problems, overall and for separate types of problems, in a large cohort of MP pre-school children and to compare the occurrence with term-born controls. Furthermore, we assessed these problems by gender.

METHODS

Study design

The "Longitudinal Preterm Outcome Project" (Lollypop) is a large prospective cohort study designed to investigate the growth, development, and general health of children born preterm, with a special focus on MP children.[19] The Lollypop cohort consists of a community-based sample of MP children (all born between 32 and 36 weeks' gestation), and a random sample of term-born children. At the stage in which the study was designed, MP children concerned those children born at 32-35 weeks gestation and therefore children born at 36^0-36^6 weeks gestation were not included. Parents completed the questionnaire on behavioural and emotional problems just before the scheduled Preventive Child Health Care (PCH) visit at four years of age. The study was approved by the local institutional review board.

Population

The study children were sampled in 13 randomly selected PCH centres, which together monitored 45,446 children. This concerns 25% of all children of this age monitored by PCH centres. In the Netherlands 90-95% of children are seen regularly by PCH centres for well-child care from birth up to age four, free of charge.[20] Guidelines of the National Centre for PCH (www.ncj.nl) are being used for monitoring in the PCH centres. Each PCH centre provided a sample of all preterm children born during one year, either from January 2002 to January 2003 or from June 2002 to June 2003. Term-born children were sampled from the same PCH centres and were in the same age range as the preterm children. After the file of each second preterm child had been drawn, the first subsequent file of a term-born child was drawn to serve as a control. Exclusion took place if a child had a congenital malformation or syndrome and if the gestational age could not be verified. For this study children born at less than 32 weeks of gestation were also excluded. Gestational age was calculated by using the last date of menstruation, and confirmed by early ultrasound measurements in >95% of cases. Parents were willing to participate for 995 (86.9%) of the MP and 577 (85.6%) of the term-born children. Response rates on the behavioural questionnaire were high: the parents of 93.3% of MP and 95.1% of term-born children returned the questionnaires.

Measures and procedure

Behavioural and emotional problems were measured using the Child Behavior Checklist (CBCL) for ages 1.5-5.[21, 22] The CBCL 1.5-5 has good psychometric properties and is widely used in diverse service settings and in research.[22] The reliability and validity of the problem scales have been confirmed for the Dutch version of the CBCL.[23, 24] It consists of 99 problem items and one open-ended item for writing down other problems, not listed on the form. Each item can be rated by the parent as follows: 0, not true; 1, somewhat or sometimes true; or 2, very true or often true. We computed seven syndrome scales by summing the ratings for the items that comprise each syndrome. Subsequently, problem scores were subdivided in three categories: normal range (<93th percentile); subclinical or borderline range (93rd to 97th percentile); and clinical or elevated range (>97th percentile). Furthermore, two broad-band groups, internalizing and externalizing problems, and the total problems score were computed. For these scores cut-offs for subclinical and clinical problems were set at the 84th and 90th percentiles, following the CBCL manual.[21] Internalizing problems consist of syndrome scales for emotionally reactive behaviour, anxious/depressed behaviour, somatic complaints, and withdrawn behaviour. Externalizing problems consist of syndrome scales for attention problems and aggressive behaviour.

Data on background characteristics were collected by a general parental questionnaire that was sent to the parents simultaneously with the CBCL. The questionnaire consisted of questions about medical conditions of the mother during pregnancy, delivery, developmental and medical conditions of the child, family composition, and socioeconomic status. Furthermore, for all children, retrospective data files from PCH centres, paediatricians, midwives, and obstetricians were available. In this way, it was possible to check some important variables such as gestational age and birth weight in more than two data files. When contradictions were found, these were checked by information in discharge letters.

Analysis

We compared behavioural and emotional problems as measured by the CBCL for MP and term-born children at pre-school age. First, characteristics (i.e., small for gestational age, gender, age of the child at completing the CBCL, family composition, number of siblings, maternal age, educational level, and ethnicity) between MP and term-born children were compared using chi-square tests.

Second, mean scores were computed for all CBCL scales to identify behavioural problems associated with moderate prematurity. In addition, differences in mean CBCL scores by gender were examined between MP and term-born children, using t-tests. All t-tests were confirmed by nonparametric Mann-Whitney U tests because of the non-Gaussian distribution of the CBCL scores. Third, we computed the risk for clinical CBCL problem scores in MP versus term-born children, using logistic regression analyses. In a multivariate logistic regression model, results were adjusted for differences in characteristics between the samples. For all statistical analyses SPSS for Windows 16.0 was used. A *P*-value of less than 0.05 was considered as statistically significant. A Bonferroni correction for multiple t-tests in our gender-subgroup would adjust the cut-off for statistical significance to 0.005.

RESULTS

Background characteristics of the preterm and term groups differed with high statistical significance regarding gender, family composition, and number of siblings, and marginally so for maternal age and educational level (*Table 1)*.

Table 2 shows that MP children had higher mean scores on internalizing (mean difference [MD], 95% confidence interval [CI]: 1.33, 0.67-1.98), externalizing (MD 1.41, 95% CI 0.59-2.23), and total problems (MD 4.04, 95% CI 2.08-6.00) than term-born children. For the syndrome scales the greatest differences were seen in withdrawn behaviour (MD 0.29, 95% CI 0.13-0.44) and attention problems (MD 0.59, 95% CI 0.39-0.79). Adjustment for gender, family composition, number of siblings, maternal age, and maternal educational level did not change the computed differences in means (*not shown*). Nonparametric testing led to similar results.

Differences in mean CBCL scores between groups tended to be greater in boys than in girls, as presented in *Table 3*. However, the gender-by-group interaction was not statistically significant. Among boys, mean scores on two syndrome scales, sleep problems and attention problems, were significantly higher in MP than in term-born children. Among MP girls, mean scores on all seven syndrome scales, as well as on internalizing, externalizing, and total problems were significantly higher than among term-born girls (*Table 3*).

Table 1 Characteristics of moderately preterm and term-born children

	Preterm (n=916)	**Term (n=543)**	*P* value
Mean gestational age (weeks)	34.0 (SD 1.0)	39.6 (SD 1.0)	
Mean birth weight (grams)	2244 (SD 465)	3553 (SD 488)	
	% (n)	*% (n)*	
Gestational age (weeks)			
32	11.5 (105)		
33	20.1 (184)		
34	27.8 (255)		
35	40.6 (372)		
38		17.1 (93)	
39		26.2 (142)	
40		35.9 (195)	
41		20.8 (113)	
SGA*	9.2 (84/916)	7.7 (42/543)	0.4
Gender (male)	57.2 (524/916)	49.2 (267/543)	0.003
Age of child (months)†			0.6
< 43	0.9 (7/768)	0.6 (3/467)	
43-47	89.6 (688/768)	91.4 (427/467)	
> 47	9.5 (73/768)	7.9 (37/467)	
Family composition			0.005
Two-parent family	92.7 (845/912)	96.3 (517/537)	
One-parent family	7.3 (67/912)	3.7 (20/537)	
Number of siblings			0.006
0	18.6 (170/916)	12.5 (68/543)	
1	54.5 (499/916)	55.2 (300/543)	
2	20.7 (190/916)	23.2 (126/543)	
≥ 3	6.2 (57/916)	9.0 (49/543)	
Maternal age (years)			0.05
< 25	8.5 (75/885)	6.1 (32/526)	
25-34	73.6 (651/885)	71.5 (376/526)	
> 34	18.0 (159/885)	22.4 (118/526)	
Maternal educational level‡			0.08
Low	30.5 (278/912)	25.6 (138/539)	
Medium	43.0 (392/912)	43.6 (235/539)	
High	26.5 (242/912)	30.8 (166/539)	
Maternal ethnicity			0.6
Netherlands	94.2 (856/909)	95.1 (507/533)	
Europe	1.8 (16/909)	1.9 (10/533)	
Outside of Europe	4.1 (37/909)	3.0 (16/533	

*SGA, small for gestational age; i.e. birth weight below the 10th percentile of the Dutch Kloosterman growth charts

† Age at completing the Child Behavior Checklist

‡ Low, primary school or less and/or low-level technical and vocational training; medium, high school or medium-level technical and vocational training for 12-16 years; high, university or high-level technical and vocational training for > 16 years

Table 2 Differences in mean Child Behavior Checklist scores between moderately preterm and term-born children

CBCL problems scale	Preterm (n=916)		Term (n=543)			
	Mean	SD	Mean	SD	Difference (95% CI)	*P*-value*
Total problems	30.40	19.41	26.36	17.80	4.04 (2.08-6.00)	< 0.001
Externalizing problems	12.44	8.12	11.03	7.50	1.41 (0.59-2.23)	< 0.01
Internalizing problems	7.93	6.71	6.60	5.85	1.33 (0.67-1.98)	< 0.001
Emotionally reactive	2.75	2.67	2.34	2.31	0.41 (0.15-0.67)	< 0.01
Anxious/depressed	1.78	2.06	1.43	1.74	0.35 (0.15-0.55)	< 0.01
Somatic complaints	2.05	2.22	1.77	1.96	0.28 (0.06-0.50)	< 0.01
Withdrawn	1.35	1.52	1.07	1.38	0.29 (0.13-0.44)	< 0.001
Sleep problems	2.03	2.34	1.62	2.11	0.41 (0.18-0.65)	< 0.01
Attention problems	2.40	2.02	1.81	1.84	0.59 (0.39-0.79)	< 0.001
Aggressive behaviour	10.04	6.75	9.22	6.17	0.82 (0.14-1.50)	< 0.05

* *P*-values calculated by t-tests; non-parametric testing provided the same significance of *P*-values for all differences, except for somatic complaints (p=0.051) and aggressive behaviour (p=0.054)

Table 3 Differences in mean Child Behavior Checklist scores between moderately preterm and term-born children by gender

	Boys				Girls			
CBCL problems scale	Preterm (n=524)	Term (n=267)	Difference (95% CI)	*P*-value*	Preterm (n=392)	Term (n=276)	Difference (95% CI)	*P*-value*
Total problems	30.99	28.52	2.47 (-0.36-5.30)	0.08	29.60	24.26	5.34 (2.59-8.09)	< 0.001
Externalizing problems	13.09	12.57	0.53 (-0.69-1.74)	0.39	11.56	9.54	2.03 (0.92-3.13)	< 0.001
Internalizing problems	7.64	6.95	0.69 (-0.24-1.61)	0.14	8.32	6.26	2.05 (1.08-3.03)	< 0.001
Emotionally reactive	2.77	2.54	0.23 (-0.15-0.62)	0.22	2.71	2.14	0.58 (0.21-0.94)	< 0.01
Anxious/depressed	1.65	1.48	0.17 (-0.09-0.43)	0.22	1.95	1.38	0.57 (0.26-0.88)	< 0.001
Somatic complaints	1.93	1.75	0.18 (-0.13-0.49)	0.25	2.21	1.79	0.42 (0.10-0.75)	< 0.05
Withdrawn	1.29	1.18	0.11 (-0.11-0.33)	0.35	1.44	0.96	0.48 (0.27-0.69)	< 0.001
Sleep problems	2.01	1.55	0.46 (0.13-0.79)	< 0.01	2.07	1.69	0.38 (0.03-0.73)	< 0.05
Attention problems	2.56	2.05	0.51 (0.21-0.81)	< 0.01	2.19	1.58	0.61 (0.33-0.89)	< 0.001
Aggressive behaviour	10.53	10.52	0.02 (-0.99-1.02)	0.98	9.38	7.96	1.42 (0.51-2.32)	< 0.01

* *P*-values calculated by t-tests; non-parametric testing provided the same significance of *P*-values for all differences except for aggressive behaviour (p=0.016) and externalizing behaviour (p=0.002) in girls, and attention problems (p=0.001) in boys

Prevalence rates of subclinical and clinical CBCL problem scores are presented in *Figure 1a-1c*. Among all MP children, 6.8% had a total problems score in the subclinical range, and 7.9% in the clinical range (combined 14.6%). For term-born children, these figures were 4.8%, and 4.6% respectively (combined 9.4%), *Figure 1a*. Total problem scores in the clinical range were more prevalent in MP boys than in MP girls (9.0% versus 6.4%), *Figure 1b and 1c*. The risk for a clinical total problems score compared with term-born peers was lower for MP boys (odds ratio [OR] 1.52, 95% CI 0.84-2.75) than for MP girls (2.62, 1.09-6.26). In MP boys, the prevalence rates of elevated externalizing problem scores were highest (9.0% subclinical and 10.5% clinical), while in MP girls the prevalence rates of elevated internalizing problem scores were highest (8.4% subclinical and 9.9% clinical).

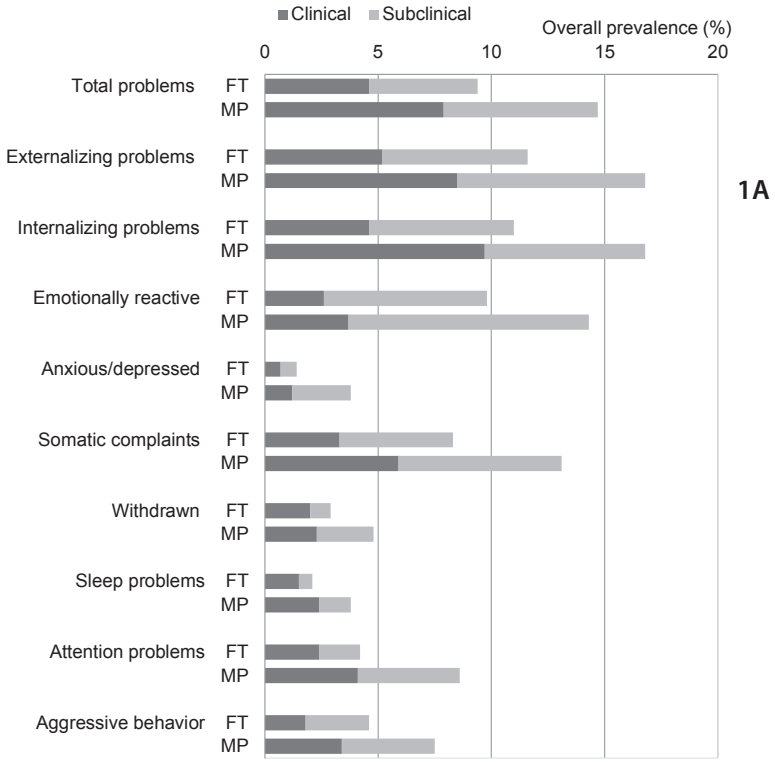
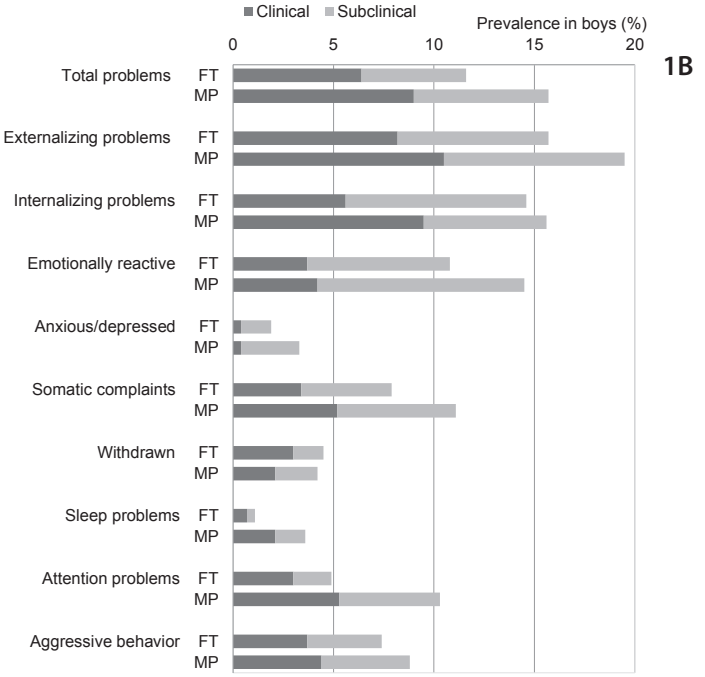
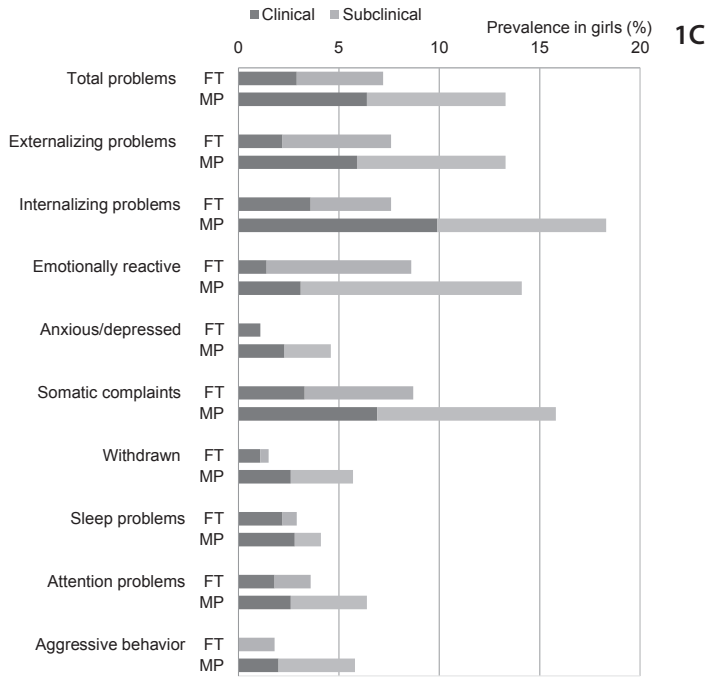


Figure 1 Prevalence rates of behavioural and emotional problems in moderately preterm (MP) and fullterm (FT) children. For total, externalizing and internalizing problems, 'clinical' indicates scores > 90th percentile and 'subclinical' indicates scores >84th and <90th percentiles. For the syndrome scales, 'clinical' indicates scores >97th percentile and 'subclinical indicates scores >93th and <97th percentiles. (A) Overall prevalence, (B) Prevalence in boys, and (C) Prevalence in girls.


Clinical
Subclinical
Prevalence in boys (%)
0
5
10
15
20
Total problems
Externalizing problems
Internalizing problems
Emotionally reactive
Anxious/depressed
Somatic complaints
Withdrawn
Sleep problems
Attention problems
Aggressive behavior
FT
MP

1B


Clinical
Subclinical
Prevalence in girls (%)
0
5
10
15
20
Total problems
Externalizing problems
Internalizing problems
Emotionally reactive
Anxious/depressed
Somatic complaints
Withdrawn
Sleep problems
Attention problems
Aggressive behavior
FT
MP

1C

Finally, in *Table 4*, ORs are given of the risk of MP children for clinical CBCL problem scores. Compared with term-born children, MP children were at significantly greater risk for clinical CBCL scores for total problems (OR 1.84, 95% CI 1.12-3.00), internalizing problems (OR 2.40, 95% CI 1.48-3.87), externalizing problems (OR 1.69, 95% CI 1.07-2.67), and somatic complaints (OR 1.92, 95% CI 1.09-3.38).

Table 4 Risk for clinical problem scores on the Child Behavior Checklist in moderately preterm versus term-born children

CBCL problems scale	Preterm (n=916) (%)	Term (n=543) (%)	uOR*	aOR (95% CI)†
Total problems	72 (7.9)	25 (4.6)	1.77	1.84 (1.12-3.00)‡
Externalizing problems	87 (8.5)	28 (5.2)	1.71	1.69 (1.07-2.67)‡
Internalizing problems	89 (9.7)	25 (4.6)	2.23	2.40 (1.48-3.87)‡
Emotionally reactive	34 (3.7)	14 (2.6)	1.46	1.70 (0.86-3.34)
Anxious/depressed	11 (1.2)	4 (0.7)	1.64	2.50 (0.68-9.19)
Somatic complaints	54 (5.9)	18 (3.3)	1.83	1.92 (1.09-3.38)‡
Withdrawn	21 (2.3)	11 (2.0)	1.14	1.38 (0.62-3.09)
Sleep problems	22 (2.4)	8 (1.5)	1.65	1.88 (0.79-4.49)
Attention problems	38 (4.1)	13 (2.3)	1.76	1.80 (0.90-3.59)
Aggressive behaviour	31 (3.4)	10 (1.8)	1.87	2.03 (0.95-4.36)

* unadjusted odds ratio

† adjusted odds ratio with 95% confidence interval; adjustment for gender, family composition, number of siblings, maternal age, and maternal educational level

‡ significant differences ($P<0.05$)

DISCUSSION

In this study, we have provided evidence that behavioural and emotional problems occur more frequently in MP than in term-born children at pre-school age. The syndrome scales emotionally reactive, anxious/depressed, somatic complaints, withdrawn behaviour, sleep problems, attention problems, and aggressive behaviour were all associated with moderate prematurity. Furthermore, we found that MP children were at greater risk for clinical CBCL scores on total problems, internalizing and externalizing problems, and on somatic complaints.

Our finding that MP children have more behavioural and emotional problems confirms the findings of most previous studies, but in a much larger sample, and at a different age.[12-16] In this study MP children had significantly worse scores than term-born children on all subscales, internalizing, externalizing, and total problems. Two previous studies also reported more internalizing behaviour

problems in MP children,[13, 14] and three studies reported more problems within the hyperactivity spectrum such as attention problems.[13, 14, 16] In addition, we found significantly more externalizing behaviour problems in MP children, in contrast to the findings of Van Baar et al. in 7-9-year-old Dutch children, and we also found more withdrawn behaviour problems.[13] These differences may have gone unnoticed in those earlier studies because those had much smaller samples. However, the reported differences apparently do have clinical relevance, as odds ratios for MP children compared to term-born children were in a similar range as previously reported for very preterm and very low birth weight (VP/VLBW) children.[26] Only one study reported no differences between children born at 34-36 weeks and term-born children for externalizing, internalizing, aggressive, and anxious/depressed problems.[12] This may be due to the restriction of that study to relatively healthy children from high-income families. The deleterious effects of preterm birth may be stronger among children born in poor families.[25]

Differences in behavioural and emotional problems by gender have previously been reported in studies on VP/VLBW children. Overall, VP/VLBW girls seem to have more internalizing problems, such as withdrawn behaviour, while VP/VLBW boys seem to be more susceptible to externalizing behaviour problems, especially in terms of attention problems.[26-29] We found the same pattern of internalizing and externalizing problems in MP girls and boys but not in term-born children. Among term-born children, both internalizing and externalizing problems were more prevalent in boys than in girls. On most syndrome scales prevalence rates were also higher in term-born boys, except for anxious/depressed and sleep problems. To summarize, moderate preterm birth seems to have a greater effect on behavioural and emotional outcomes in girls than in boys. However, on total problems prevalence rates among girls did not differ much compared to rates among term-born boys. It still serves additional research why prematurity would affect behavioural and emotional outcomes more in girls than in boys. Currently, we have no real explanation for it. Differences in background characteristics could not explain these findings.

The important strengths of this study were its large community based sample, the collection of data in a similar way among MP and term-born children, and its high response rate. Moreover, this is the first study investigating the full range of behavioural and emotional problems in MP children just before they enter school. For measurement of behavioural and emotional problems the CBCL was used, which is a valid and widely used questionnaire.[21] A large number of parents returned the CBCL questionnaires.

One potential limitation of this study is that we did not obtain a professional assessment of the behavioural and emotional problems. If the observations of professionals could have been compared with parents' observations, the results of this study would have provided a more complete picture of the behavioural and emotional problems in MP children. However, parent-reported problems seem to be very important for the identification of psychosocial problems.[30] Another limitation of this study is the lack of information on some early risk factors for behavioural and emotional problems, such as maternal depression and preschool educational experience. Further research is needed to determine the joint effects of maternal psychological, obstetrical, and environmental factors on behavioural and emotional problems.

Conclusion

Our results demonstrate that MP children are more likely to have behavioural and emotional problems already at pre-school age. Therefore, MP children could be a potential target group for prevention of mental health problems, as behavioural and emotional problems in early childhood tend to persist in later childhood and adolescence.[31-33] Moreover, mental health problems have a great impact on the developmental and social competencies at school and in the community.[31-33] Interventions at early school age might, for example, include extra support at school or even specialized school services, along with psychological assistance. Our findings need to be confirmed by other studies, as we were the first to assess the full range of behavioural and emotional problems in MP children just before they enter school.

Acknowledgements

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Chapter 4

Behavioural and emotional problems in moderately preterm children with low socioeconomic status: a population-based study

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ABSTRACT

Background Moderately preterm (MP) birth is associated with higher rates of behavioural and emotional problems. To determine the extent to which low socioeconomic status (SES) contributes to these higher rates, we assessed independent and joint effects of MP birth and low SES, overall and by gender.

Methods Dutch preventive child health care centres provided a population-based sample of 915 MP children (32-36 weeks' gestation) and 543 term-born children, born in 2002/2003. In multivariable logistic regression analyses, we determined the risk of behavioural and emotional problems per standard deviation (SD) decrease in gestational age and SES, using standardized measures for both. We also assessed three SES categories, being low (1SD or more below mean of standardized SES), intermediate (mean+/-1SD), and high (greater than mean+1SD). The Child Behavior Checklist for 1.5-5 years was used to assess behavioural (externalizing), emotional (internalizing), and total problems at age 4 years.

Results MP children with low SES had significantly higher total problem scores than those with high SES (11.3% vs. 5.1%, respectively). Each SD decrease in SES was associated with a 42% higher odds of elevated total problem scores (OR 1.42, 95% CI 1.14-1.77). No joint effects were found, meaning that lower gestational age independently added to the risk of behaviour problems (OR 1.24, 95% CI 1.00-1.56). Effects of MP birth and low SES were more pronounced in girls.

Conclusions MP birth and low SES multiply the risk of behavioural and emotional problems. The combination of risk factors identifies children who could benefit greatly from early intervention.

INTRODUCTION

Moderately preterm (MP) children, born at 32 to 36 weeks' gestation, are at greater risk of behavioural and emotional problems than term-born children.[1-3] Risks increase with decreasing gestational age, but 85% of preterm children are born after 32 weeks' gestation.[4,5] As a consequence, children born moderately to late preterm contribute most to the societal burden associated with preterm birth.[6]

Although 8-10% of 4-year-old MP children struggle significantly with behavioural and emotional problems,[3] the majority of MP children do not exhibit any difficulties. For some extent, this may be explained by differences in socioeconomic status (SES). Children from low SES families are more likely to face multiple adversities, putting them at considerable higher risk of behavioural and emotional problems.[7] Moreover, MP children are more frequently confronted with socioeconomic-related adversities than term-born children because preterm birth is more likely to occur in deprived areas than in prosperous ones.[8-10] Several mediating factors may have a share in this link between low SES and preterm birth. For example, lifestyle-associated factors, such as smoking, increase the risk of spontaneous preterm labour.[8,10] In addition, women with low SES are more likely to experience psychosocial stress, a significant and independent risk factor for preterm birth[5,8,11] and for behavioural and emotional problems in preterm-born offspring.[12]

Next to SES, gender also seems to be an important determinant of the occurrence of behavioural and emotional problems in preterm children.[3,13,14] Overall, preterm boys tend to have more externalizing and attention problems, while preterm girls tend to be more susceptible to internalizing problems, such as withdrawn behaviour.[13] However, interrelationships of gender with MP birth and low SES remain unclear.

It is unknown to what extent low SES contributes to the higher prevalence of behavioural and emotional problems observed in MP children. If MP birth and low SES multiply each other's risk of behavioural and emotional problems, this combination of risk factors may identify the MP children who are in greatest need of early intervention.[15,16] Therefore, the aim of this study was to determine the independent and joint effects of MP birth and low SES on behavioural and emotional problems in a large population-based sample, with a special focus on gender differences.

METHODS

Study design

This study is part of the Longitudinal Preterm Outcome Project (LOLLIPOP), a Dutch prospective cohort study designed to investigate growth, development, and general health of preterm-born children, with particular attention to MP children born at 32^0 to 35^6 weeks of gestation.[17] LOLLIPOP consists of a community-based sample of preterm children and a matched random sample of term-born controls (38^0 to 41^6 weeks of gestation). The 4-year-old participants were recruited from 13 randomly selected preventive child health care (PCH) centres across the Netherlands, covering urban and rural areas. Together these centres covered the care for 45,446 children, representing 25% of all 4-year-olds monitored by Dutch PCH centres. In the Netherlands, 90% to 95% of children are seen regularly and free of charge by PCH professionals for well-child care from birth up to 4 years of age.[18] PCH professionals, i.e. doctors and nurses, monitor mental and physical development through structured interviews with parents, general physical examinations, and standardised screening procedures, all of which are documented in PCH files. The study was approved by the review board of the University Medical Center Groningen, and written informed consent was obtained from the parents of study participants.

Sampling procedure

MP children were sampled from a community-based cohort of 45,455 children born in 2002 and 2003. We based the size of the sample on estimates of the numbers needed to compile growth curves for Dutch preterm-born children, because for that part of the LOLLIPOP study we needed the largest number of children. Each of the 13 PCH centres provided a sample of preterm children and term-born controls of the same age-range, based on their card files. After the file of each second preterm child had been selected, the file of the next term-born child served as a control. Children were excluded if they had congenital malformations or syndromes, if the gestational age could not be verified or was beyond of the set range, or if families had moved between sampling and inclusion. An overview of the sampling procedure of LOLLIPOP was previously provided.[17] In short, out of 1145 eligible MP children, 995 parents (86.9%) agreed to participate in the long-term follow-up part of the study, and of the 674 eligible term-born children, 577 (85.6%) parents agreed to participate. Response rates among parents of the fully

participating MP and term-born children were 93.3% and 95.1%, respectively. This led to a total of 1458 children in this study: 915 MP children and 543 term-born children.

Assessment of socioeconomic status

We determined SES on the basis of the three most frequently used measures, i.e. education, income, and occupation.[19,20] Data on the highest completed educational level of both parents were collected by a general questionnaire when the participating children were aged 4 years. The following categories were defined: primary school or less, low-level technical and vocational training (<12 years' education), high school or medium-level technical and vocational training (12 to 16 years' education), and university or high-level technical and vocational training (>16 years' education). At the same time, parents were asked to indicate their net monthly family income in euros: ≤ 850; 851 to 1150; 1151 to 1750; 1751 to 3050; 3051 to 3500; and > 3500. Data on occupational level were collected retrospectively from the medical birth registers kept by the PCH centres. We classified the occupational level of both parents according to the International Standard Classification of Occupations.[21] Next, we computed a composite SES score on the basis of five indicators: educational level of father, educational level of mother, family income, occupational level of father, and occupational level of mother. Information on these indicators was available for 96%, 99%, 77%, 82%, and 72% of the participating children, respectively. We ranked and standardised each of the indicators and computed the mean SES, with all indicators that were available for each child. Subsequently, a composite and standardized SES measure was computed, a continuous variable with a mean of 0 and a standard deviation (SD) of 1. Additionally, for descriptive purposes, we determined three categories of SES: 1) low, scores more than 1 SD below the mean of the standardized SES; 2) intermediate, scores between mean +/- 1 SD; and 3) high, scores greater than mean + 1 SD.

Behavioural and emotional outcomes

We measured behavioural and emotional problems at age 4 years, using the Dutch version of the Child Behavior Checklist (CBCL) for 1.5-5 years.[22,23] This checklist has good psychometric properties and is widely used in a variety of health care settings and for research purposes.[23] The reliability and validity of the problem scales were confirmed for the Dutch version of the CBCL.[22,25] It consists of 99

problem items and one open-ended item for recording any problems not listed on the form. Each item can be rated as either: 0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true. By summing the ratings for sets of items, we computed internalizing and externalizing problems, and a total problems score. We used the American cut-offs based on the guidelines for the CBCL regarding cross-cultural comparisons. In the guidelines is written that for Dutch children the same cut-offs are advised as in American children.[22]

Covariates

Data on background characteristics were collected using a general parental questionnaire that was sent to the parents simultaneously with the CBCL. The questionnaire consisted of questions about pregnancy, delivery, developmental and medical conditions of the child, family composition, and socioeconomic status. Furthermore, retrospective medical files for all children were available from PCH centres, paediatricians, midwives, and obstetricians. The most important variables (e.g. gestational age) from the parental questionnaires were crosschecked with information from the medical records. In more than 95% of cases, gestational age was calculated by using the last date of menstruation, and confirmed by early ultrasound measurements. When inconsistencies were found, these were checked against information in discharge letters.

Statistical analyses

First, we assessed child and family characteristics of the study participants categorized by low, intermediate, and high SES. Next, we examined prevalence rates of clinically relevant CBCL scores in MP children according to SES categories. Third, we performed logistic regression models to examine independent and joint effects of MP birth and SES on behavioural and emotional problems. In these analyses we used standardised measures for gestational age and SES, meaning that both risk factors had a mean of 0 and a SD of 1. In the first logistic regression model, we included MP birth and SES, mutually adjusting for their effects on behavioural and emotional problems. In the second model we assessed whether MP birth and low SES had joint effects on CBCL outcomes by adding the MP birth * SES interaction. In the case of joint effects, the combination of MP birth and low SES would be less meaningful because of shared effects (adversities do not multiply in that case). In the third and final model, we adjusted for the effect of potential confounders which we had identified in relevant literature and

differences in background characteristics. To prevent over-adjustment for factors that highly correlated with SES, we did not adjust for family composition and mothers' ethnicity. Finally, we conducted stratified analyses by gender because in previous work girls appeared to be more vulnerable than boys for the effects of MP birth.[3] Statistical analyses were performed in SPSS for Windows v. 20.0 (Chicago, Illinois).

RESULTS

In *Table 1* we present characteristics of the study participants according to SES. In our sample of 915 MP and 543 term-born children, the rate of MP birth was 71.8% in children with low SES, 61.7% in children with intermediate SES, and 57.6% in children with high SES. The background characteristics that differed significantly between SES categories were family composition, number of siblings, age of mother, and ethnicity of mother. Children with low family SES were more likely to be part of a one-parent family, to have many siblings, to have a young mother (< 25 years of age), and to have a non-European mother. Non-participating children differed from participating children regarding some characteristics shown in *Table 1*. Low SES was more common among non-participating children (educational level and non-Dutch ethnicity both $P < .001$). Gender and SGA did not differ significantly between participating and non-participating children.

Table 2 shows the prevalence rates of clinically relevant CBCL scores in MP and term-born children. In all three SES categories, prevalence rates were highest in MP children. Furthermore, the prevalence of behavioural and emotional problems increased markedly with decreasing SES. Regarding total problems, prevalence rates in MP children increased from 5.1% (high SES) to 7.5% (intermediate SES) and 11.3% (low SES). MP children with low SES had significantly higher total problem scores than those with high SES (P=0.013).

Table 1 Characteristics of study participants according to socioeconomic status[a]

Variable	Low SES	Intermediate SES	High SES	*P* value
Total % (*n*)	17.8 (259)	63.6 (928)	18.6 (271)	
Variable, % (*n*)				
MP birth	71.8 (186)	61.7 (573)	57.6 (156)	.002
SGA (< P10)[b]	10.0 (26)	8.3 (77)	8.5 (23)	.67
Male gender	58.7 (152)	53.4 (496)	52.4 (142)	.26
Age of child (months)[c]				.54
43-47	91.6 (186)	90.5 (711)	88.6 (218)	
< 43 or > 47	8.4 (17)	9.5 (75)	11.4 (28)	
Family composition				
Two-parent family	87.7 (222)	94.4 (874)	98.5 (266)	< .001
One-parent family	12.3 (31)	5.6 (52)	1.5 (4)	
Number of siblings				
0	19.3 (50)	16.2 (150)	13.7 (37)	.037
1	48.6 (126)	56.0 (520)	56.5 (153)	
2	20.5 (53)	21.6 (200)	23.2 (63)	
≥ 3	11.6 (30)	6.3 (58)	6.6 (18)	
Age of mother				
< 25	13.1 (32)	8.0 (72)	1.1 (3)	< .001
25-34	67.8 (166)	74.2 (668)	72.5 (192)	
> 34	19.2 (47)	17.8 (160)	26.4 (70)	
Ethnicity of mother				
Netherlands	89.3 (226)	95.1 (876)	97.4 (261)	< .001
European	0.8 (2)	2.2 (20)	1.5 (4)	
Non-European	9.9 (25)	2.7 (25)	1.1 (3)	
Education of mother[d]				< .001
Low	7.8 (20)	0.4 (4)	-	
Low to intermediate	83.2 (213)	19.3 (179)	-	
Intermediate to high	9.0 (23)	61.2 (567)	13.8 (37)	
High	-	19.0 (176)	86.2 (232)	
Education of father[d]				< .001
Low	10.7 (24)	1.1 (10)	-	
Low to intermediate	79.6 (179)	26.7 (242)	0.4 (1)	
Intermediate to high	9.8 (22)	51.2 (465)	9.7 (26)	
High	-	21.0 (191)	90.0 (242)	
Family income, euro[d]				< .001
< 850	5.5 (10)	0.6 (4)	-	
851 - 1150	24.3 (44)	3.1 (22)	-	
1151 - 1750	42.5 (77)	15.3 (110)	-	
1751 - 3050	27.6 (50)	68.2 (489)	27.1 (61)	
3051 - 3500	-	9.1 (65)	24.4 (55)	
≥ 3501	-	3.8 (27)	48.4 (109)	

[a] Low SES, scores ≤ mean - 1 SD on standardised SES scale; intermediate SES, scores > mean - 1 SD and ≤ mean + 1 SD; high SES, scores > mean + 1 SD.

[b] SGA, small for gestational age; i.e. birth weight below the 10th percentile of the Dutch Kloosterman growth charts.

[c] Age at completing the Ages and Stages Questionnaire; uncorrected calendar age.

[d] Extensive information on SES indicators is defined in the Methods section.

Table 2 Prevalence rates of clinically relevant CBCL scores[a] in moderately preterm (MP) and term-born children according to socioeconomic status (SES)

CBCL Outcome	Low SES[b]	Intermediate SES	High SES
Outcome, % (n/N)			
Total problems			
Term-born	5.5 (4/73)	5.1 (18/355)	2.6 (3/115)
MP	11.3 (21/186)	7.5 (43/573)	5.1 (8/156)
Externalizing			
Term-born	5.5 (4/73)	5.6 (20/355)	3.5 (4/115)
MP	10.8 (20/186)	8.2 (47/573)	7.1 (11/156)
Internalizing			
Term-born	9.6 (7/73)	4.2 (15/355)	2.6 (3/115)
MP	11.3 (21/186)	10.3 (59/573)	5.8 (9/156)

[a] Clinically relevant Child Behavior Checklist (CBCL) scores: scores higher than the cut-off at the 90th percentile.
[b] Low SES, 1 SD or more below the mean of the standardised SES; intermediate SES, scores between mean - 1 SD and mean + 1 SD; high SES, scores + 1 SD or more above the mean.

Table 3 shows the ORs and 95% CIs for clinically relevant CBCL scores per SD decrease in SES and MP birth (per SD gestational age). We used standardised values for SES and MP birth, with lower values indicating higher risk. The univariate ORs were hardly affected by mutual adjustment for SES and MP birth (Model 1). In Model 2 we added the SES * MP birth interaction in order to assess joint effects of the risk factors. No statistically significant effects were found, which meant that effects of SES and MP birth were multiplicative (as is the case for any logistic model without interactions). Finally, in Model 3 we adjusted the ORs of Model 1 for gender, number of siblings, and maternal age. This hardly affected the point estimates.

Table 3 Odds ratios (95% confidence intervals) for behavioural and emotional problems: effects of socioeconomic status (SES) and moderately preterm (MP) birth in three multivariate logistic regression models

CBCL Outcome	Univariate	Model 1	Model 2	Model 3
Score, OR (95% CI)[a]				
Total problems				
SES	1.38 (1.12 - 1.70)***	1.36 (1.10 - 1.68)***	1.48 (1.15 - 1.92)***	1.42 (1.14 - 1.77)***
MP birth	1.29 (1.03 - 1.61)*	1.26 (1.01 - 1.57)*	1.40 (1.04 - 1.88)*	1.24 (1.00 - 1.56)
SES*MP birth			0.83 (0.60 - 1.15)	
Externalizing				
SES	1.20 (0.98 - 1.46)	1.17 (0.96 - 1.43)	1.23 (0.95 - 1.59)	1.21 (0.99 - 1.50)
MP birth	1.33 (1.07 - 1.64)**	1.31 (1.06 - 1.62)*	1.37 (1.04 - 1.80)*	1.31 (1.05 - 1.63)*
SES*MP birth			0.92 (0.66 - 1.27)	
Internalizing				
SES	1.28 (1.06 - 1.55)*	1.25 (1.03 - 1.52)*	1.45 (1.14 - 1.85)***	1.26 (1.03 - 1.54)*
MP birth	1.43 (1.16 - 1.77)***	1.40 (1.14 - 1.74)***	1.64 (1.25 - 2.16)***	1.41 (1.13 - 1.73)***
SES*MP birth			0.76 (0.56 - 1.02)	

Levels of significance: * indicates $p < .05$, ** indicates $p < .01$, and *** indicates $p < .005$
Model 1: assessing the effects of socioeconomic status (SES) and moderately preterm (MP) birth in a multivariate model.

Model 2: assessing joint effects of SES and MP birth, by adding the SES*MP birth interaction to Model 1.
Model 3: adjusting Model 1 for gender, number of siblings, and maternal age.
[a] Odds ratios represent the risk per SD decrease in SES and MP birth (i.e. gestational age), respectively, with lower values indicating higher risk.

In analyses stratified by gender, ORs were greater among girls than among boys, especially regarding the effects of low SES (*Table 4*). The OR for externalizing was 2.23 (95% CI 1.46-3.38) in girls compared to 1.15 (95% CI 0.88-1.50) in boys per SD decrease in SES, and for internalizing the OR was 1.43 (95% CI 1.03-1.98) compared to 1.16 (95% CI 0.89-1.52), respectively.

Table 4 Odds ratios (95% confidence intervals) for behavioural and emotional problems: effects of socioeconomic status (SES) and moderately preterm (MP) birth, stratified by gender

CBCL Outcome	**Overall** (N = 1458)	**Boys** (n = 790)[a]	**Girls** (n = 668)[a]
Score, OR (95% CI)[b]			
Total problems			
SES	1.42 (1.14 - 1.77)***	1.15 (0.88 - 1.50)	2.23 (1.46 - 3.38)***
MP birth	1.24 (1.00 - 1.56)	1.24 (0.93 - 1.64)	1.24 (0.86 - 1.78)
Externalizing			
SES	1.21 (0.99 - 1.50)	0.99 (0.77 - 1.26)	2.09 (1.36 - 3.21)***
MP birth	1.31 (1.05 - 1.63)*	1.24 (0.95 - 1.61)	1.50 (1.00 - 2.26)
Internalizing			
SES	1.26 (1.03 - 1.54)*	1.16 (0.89 - 1.52)	1.43 (1.03 - 1.98)*
MP birth	1.41 (1.13 - 1.73)***	1.34 (1.00 - 1.79)	1.48 (1.08 - 2.04)*

Levels of significance: * indicates $p < .05$, ** indicates $p < .01$, and *** indicates $p < .005$
[a] Model 3 (Table 2): multivariate analysis with adjustment for number of siblings and maternal age.
[b] Odds ratios represent the risk per SD decrease in SES and MP birth (i.e. gestational age), respectively, with lower values indicating higher risk.

The difference between boys and girls is illustrated in *Figure 1*, showing the prevalence rates of externalizing, internalizing, and total problems in three risk subgroups (i.e. MP birth, low SES, and MP birth combined with low SES). In girls prevalence rates were clearly higher in risk subgroups (*Figure 1a*). Among girls with combined risk, for example, 13.0% had elevated scores on total problems, compared with 4.9% in girls overall. In contrast, prevalence rates in boys were hardly higher in risk subgroups than in boys overall (*Figure 1b*).

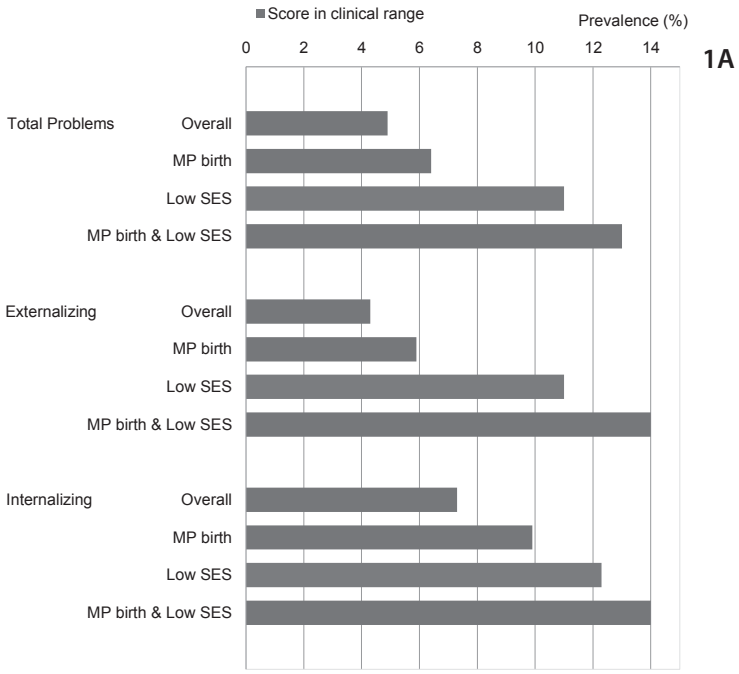
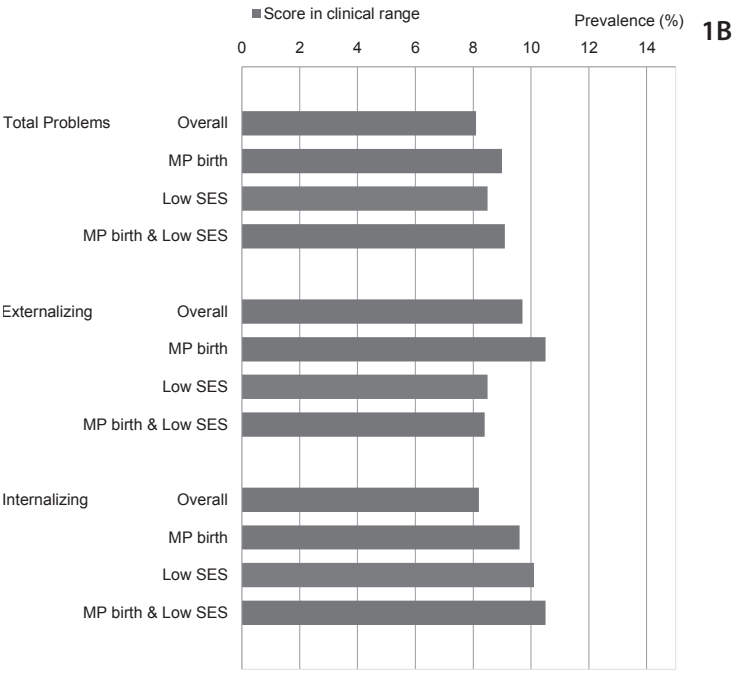


Figure 1 Prevalence rates of clinically relevant CBCL scores (>90th percentile). MP, moderately preterm; SES, socioeconomic status. **1A,** Rates in girls (n = 668). **1B,** Rates in boys (n = 790).



DISCUSSION

In this large population-based cohort study, we demonstrated that low SES and MP birth had independent, multiplicative effects on behavioural and emotional problems in 4-year-old children. We also found that boys were more likely to externalize, but girls in particular were vulnerable to the effects of MP birth and low SES.

Our finding that low SES is an independent contributor to higher rates of behavioural and emotional problems in MP children, can be interpreted in two ways. First, the results indicate that the effects of MP birth are not a reflection of low SES, also not partly. Second, low SES seems to explain why some MP children struggle more with behavioural and emotional problems than other MP children, because risks multiply. As far as we know, combined effects of SES and MP birth on behavioural and emotional problems have not been assessed before. However, prior studies have shown that low SES and preterm birth are both adverse and stressful experiences for children and their parents,[7,16,26,27] for example due to hospitalization at the neonatal intensive care unit.[28]

Exposure to multiple stressful experiences as in the case of MP children with low SES may be an explanation for higher rates of behavioural and emotional problems, either directly or indirectly, but this is speculative. In children and adults, early stressful experiences have directly been associated with altered functioning of several brain areas and regulation systems, such as the limbic system, the cerebellum, and the HPA axis.[29-31] These alterations in response to early stress may function to prepare new-borns for high levels of stress in later life, referring to the hypothesis of early programming of disease, which assumes that the perinatal period is a critical period for child development with lifelong effects on physical and mental wellbeing.[32-34]

Indirectly, chronic stressful experiences associated with preterm birth and low SES may decrease the quality of parenting and parent-child interactions, which has shown to affect socio-emotional development of 5-year-old preterm children.[27] Furthermore, in preterm children whose mother experienced the perinatal period as stressful, the impact of early adversities on behavioural problems and psychiatric disorders at preschool age is greater.[30,35,36] Even mothers of children born late preterm (34-37 weeks' gestation) experienced significantly higher levels of emotional stress than mothers of term-born children.[26] Parents of MP children may experience more emotional stress due to worry about the

child's health, anxiousness, and depressed feelings, and this may coincide with less attentive or less sensitive parenting.[26,37] As a consequence, mothers might not notice the needs of their children or, conversely, they might be over-protective.[38] Eventually, these parenting styles may lead to persistently higher behavioural and emotional symptoms across childhood.[34] Therefore, reducing emotional stress among mothers, to improve parenting quality and parent-child interactions, may prevent behavioural and emotional problems, especially in children who face multiple adversities.

Gender differences were of particular interest in this study. Male gender is a known risk factor for externalizing problems, and in particular for attention problems, also in preterm children.[13,28] This was the case in our study too, as we found a higher rate of externalizing problems among boys than among girls. However, unexpectedly, MP boys did not externalize significantly more than term-born boys (see also Potijk et al.[3]) and boys with low SES did not externalize more often than boys overall did. On the other hand, MP girls, particularly those with low SES, had considerably poorer scores on externalizing and internalizing problems than girls overall. This is in line with another study among MP children of preschool age, in which only the preterm girls had significantly more behaviour problems, i.e. attention problems and hyperactive/impulsive behaviour, than their term-born counterparts.[14] Although it seems conflicting with the fact that boys tend to have more (externalizing) problems, evidence is increasing that girls in particular are affected by preterm birth and low birth weight.[14,39,40]

Greater vulnerability of girls to MP birth and low SES might have gone unnoticed in previous studies among preterm children because sample sizes for stratification by gender were not sufficient. Moreover, in many studies mean scores have been compared instead of clinically relevant scores. In smaller cohorts, very few children have scores in the clinical range. Furthermore, the gestational and developmental age varied between studies, e.g. very preterm children aged 5,[41] MP children aged 5,[14] and very preterm children aged 8 to 19 years.[42,43] For better comparison of our findings, larger cohorts of pre-school aged MP children are needed. Until confirmation our findings by other researchers, we can only hypothesize about explanations. One explanation, for example, may be that girls are more sensible to early socio-emotional deprivation than boys.[44] Therefore, stressful emotional experiences in early childhood may affect girls more than boys, leaving long-lasting effects on mental health.[45,46]

Strengths and limitations

An important strength of this study was its large population-based sample, which was well-suited to examine the effects of both MP birth and SES. Furthermore, response rates on the CBCL were high: more than 90% of parents who participated in the long-term follow-up part of the study returned the questionnaires. Finally, the SES measure that we used was a composite score of the three most frequently used indicators of SES, i.e. occupation, education, and income.[19] Although rarely used in medical research, composite SES measures provide a good opportunity to fully account for effects that can be attributed to socioeconomic conditions.[20,47]

Our study also has some limitations to address. First, we used parental reports to assess behavioural and emotional problems. Parents are of significant value when it comes to identifying children's behavioural and emotional problems,[48] but reports from psychologists or psychiatrists would have provided a professional view on the problems. Second, the study lacked information on factors that may explain part of the effect of MP birth and/or low SES on behavioural and emotional problems, such as parental psychopathology and genetic factors. Finally, low SES was more common among non-participating children and this may have influenced our results. However, the presented effects of SES would then rather be an underestimation of the real effects.

Implications for preventive child health care (PCH)

In PCH centres, more attention should be paid to MP children with low SES, as the combination of these risk factors considerably increases the risk of behavioural and emotional problems. MP children with low SES have a greater chance of facing multiple environmental adversities in early childhood, and therefore they may profit more from interventions than MP children from higher SES backgrounds.[15,16] Indeed, one intervention study among preterm children showed that higher levels of distress at baseline were associated with greater improvements in behaviour.[15] However, further research is needed to explore the impact of interventions specifically in MP children with low SES, and to assess whether a gender-specific approach may be called for since girls seem to be more susceptible than boys to early childhood adversity.

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Chapter 5

Co-occurrence of developmental and behavioural problems in moderate to late preterm-born children

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Submitted

ABSTRACT

Objective To determine the occurrence of emotional and behavioural problems (EBP) in moderate to late preterm-born (MLP) and full-term children with developmental delay.

Design Participants were recruited from thirteen randomly selected preventive child healthcare (PCH) centres in the Netherlands. We included 903 MLP children of 32-36 weeks' gestation and 538 full-term controls, born between January 2002 and June 2003. Parents completed the Ages and Stages Questionnaire (ASQ) and Child Behavior Checklist (CBCL) shortly before the scheduled PCH visit at four years of age. In logistic regression analyses we used a composite measure of co-occurrence: ASQ total or domain score >2 SDs below the mean and a CBCL score >84th percentile on total problems, internalizing (emotional) or externalizing (behavioural) problems.

Results Among MLP children with abnormal ASQ total problems-scores, EBP were more prevalent than among full-term children, particularly regarding externalizing problems (34% vs. 24%). In MLP children, rates of EBP differed per developmental domain and were highest for domains problem-solving (36% had externalizing problems) and personal-social skills (39% had internalizing problems). The risk of any type of co-occurrence was higher for MLP than full-term children (OR 1.86; 95% CI 1.14-3.03). Independent risk factors for co-occurrence were male gender, low socioeconomic status, and young maternal age.

Conclusions Up to 39% of 4-year-old MLP children with developmental delay also have EBP. Given the low number of full-term controls with co-occurring problems, larger studies are needed to determine the independent contribution of moderate prematurity to co-occurrence, relative to other risk factors.

What is already known on this topic

- ▷ Developmental delay occurs in 6% to 11% of pre-schoolers born moderately to late preterm, compared to 4% of those born full-term.
- ▷ Early detection of co-occurrence of developmental and behavioural problems may help to identify those moderate preterm-born children most in need of early intervention.

What this study adds

- ▷ In pre-schoolers born moderately to late preterm, developmental delay co-occurs with emotional and behavioural problems in 25% to 39% of cases.
- ▷ In preventive child healthcare, increased awareness is warranted for behavioural and emotional problems in moderate and late preterm-born children with developmental delay.
- ▷ Further research is needed to determine the added value of addressing co-occurring neurodevelopmental problems at pre-school age.

INTRODUCTION

Worldwide, preterm birth occurs in 10% percent of all live births.[1] Eight out of ten preterm children are born at 32^0 to 36^6 weeks' gestation, i.e. moderate to late preterm (MLP).[2-4] Compared to full-term children, MLP children are at increased risk of neonatal morbidities, such as respiratory problems, hypoglycaemia and hyperbilirubinemia,[5] and of long-term neurodevelopmental problems, such as developmental delay and learning problems.[6-11] The risk of developmental delay is approximately twice as high in MLP than in full-term children, with developmental delay occurring in 6% to 11% of preschool-aged MLP children and 4% of full-term children, according to abnormal total scores on the Ages and Stages Questionnaire (ASQ).[9,12]

Developmental delay frequently co-occurs with emotional and behavioural problems (EBP).[13,14] For example, many children with motor and coordination problems also have attention problems, social problems, and/or psychosomatic problems.[15-17] In previous research among very preterm children (<32 weeks' gestation), high rates of co-occurring developmental problems and EBP were found.[18,19] Up to 50% of very preterm children appeared to have more than one developmental or behavioural disability at the age of five years, compared to 8% in full-term controls.[18,19] In MLP children of about the same age, however, the co-occurrence of developmental delay and EBP is unknown.

Our main aim, therefore, was to determine the co-occurrence of developmental delay and EBP in MLP children at preschool age, and to compare with full-term controls. We hypothesized that MLP children would have an increased risk of co-occurring problems since intra-uterine brain development is disrupted three to eight weeks before term gestation, which may cause changes in functional connectivity processes of neural motor networks.[20] Secondary, we aimed to explore whether other risk factors for co-occurrence could be identified.

PATIENTS AND METHODS

Study design

We derived the data for this study from the Longitudinal Preterm Outcome Project (LOLLIPOP), a large prospective cohort study in the Netherlands. LOLLIPOP was designed to investigate growth, development, and general health of preterm children, focusing mainly on MLP children. It consists of a community-based sample of MLP children and a random sample of full-term controls (38^0 to 41^6 weeks' gestation). At the time the study was designed, children born between 32 and 36 weeks' gestation were referred to as moderate preterms. Therefore, children born at 36^0 to 36^6 weeks' gestation were not included. LOLLIPOP was approved by our institutional medical ethical review board and written informed consent was obtained from all parents.

Participants and procedure

Participants were recruited from thirteen randomly selected preventive child healthcare (PCH) centres from across the Netherlands, including urban and rural areas. In the PCH centres, from birth up to four years of age, 95% of children are seen by well-child care doctors at regular moments and free of charge.[21] Together, the thirteen selected PCH centres monitored the physical and mental development of 45,446 children. At the time that was 25% of all four-year-old children monitored by the PCH centres in the Netherlands. The sample size was based on estimates of the numbers needed to compile growth curves for Dutch preterm children.[22]

Each of the PCH centres provided a sample of preterm children and full-term controls of the same age range, based on their medical files. After the file of each second preterm child had been selected, the file of the next full-term child served as a control. Children were excluded if they had major congenital malformations or syndromes, if the gestational age could not be verified or was beyond the set range, or if families had moved between sampling and inclusion. An overview of the sampling procedure of LOLLIPOP was provided previously.[9] The parents of 995 MLP children agreed to participate in the long-term follow-up part of the study, as did the parents of 577 full-term children. Regarding the fully participating children, co-occurrence of developmental delay and EBP could be determined in 903 MLP children (91.0%) and 538 full-term children (93.2%). In the majority of cases it was the mother who filled out the ASQ and CBCL.

Developmental delay

Developmental outcomes were measured using the Dutch version of the 48-month form of the ASQ, which is a validated, parent-completed screening instrument.[23,24] We computed scores on the five developmental domains of the ASQ: fine motor, gross motor, communication, problem-solving, and personal-social skills.[24] Each domain consists of six questions on developmental milestones. Parents were asked whether their child had achieved (yes, ten points), had partly achieved (sometimes, five points), or had not yet achieved (no, zero points) a certain milestone. By taking the mean of the five domain scores, we computed a total score on development. Children who had an ASQ total or domain score >2 SDs below the mean of the Dutch reference group were considered as having developmental delay.[23]

Emotional and behavioural problems (EBP)

We measured EBP using the CBCL for ages 1.5 to 5 years.[25,26] This checklist has good psychometric properties and is widely used in a variety of health care settings and for research purposes[26] in various countries including the Netherlands.[27,28] It consists of 99 problem items and one open-ended item for recording any problems not listed on the form. Each item can be rated as either 0 = not true, 1 = somewhat or sometimes true, or 2 = very true or often true. By summing the ratings for sets of items, we computed internalizing and externalizing problems, and a total problems score. In accordance with the CBCL manual,[25] we set the cut-off for subclinical and clinical problems at the 84th and 90th percentiles, respectively.

Covariates

Data on background characteristics were collected from the following sources, 1) a general parental questionnaire that was sent to the parents together with the ASQ and CBCL, and 2) medical files from PCH centres, clinical paediatricians, midwives, and obstetricians. The general questionnaire consisted of information about pregnancy, delivery, gestational age, birth weight, medical conditions of the child, family composition, ethnicity, educational level of the parents, and family income. Gestational age was calculated by using the last date of menstruation, and was confirmed by early ultrasound measurements in more than 95% of cases. For socioeconomic status we used a composite measure that consisted of education, occupation, and family income, as previously reported.[29] Important information from the parental questionnaire, such as gestational age, were cross-checked with information from the medical files. In case of inconsistencies, we checked these against information contained in discharge letters.

Statistical analyses

First, baseline characteristics of children with and without co-occurrence were compared, using *t* tests for continuous data and chi-squared tests for categorical data. Second, we assessed rates of EBP that were in the subclinical and clinical range, among MLP and full-term children with and without developmental delay. We did this for the ASQ total score and for each ASQ domain separately. Third, using logistic regression analyses, we assessed the risk of co-occurrence in MLP compared to full-term children, for which we used a composite measure of co-occurrence, i.e. an ASQ total or domain score >2 SDs below the mean and a CBCL score >84th percentile on total problems, internalizing or externalizing problems. In multivariate logistic regression analyses we added gender, socioeconomic status, maternal age, and ethnicity to the univariate model in three consecutive steps to determine whether effects of MLP birth could be explained by these factors and to explore whether other independent risk factors for co-occurrence could be identified. All statistical analyses were performed in SPSS for Windows version 22.0 (Chicago, Illinois).

RESULTS

Table 1 shows the baseline characteristics of study participants with and without co-occurrence of developmental delay and EBP. In total, 100 out of 1,441 children (6.9%) had developmental delay and EBP: 77 out of 903 (8.5%) MLP children and 23 out of 538 (4.3%) full-term children. Gender, maternal age, socioeconomic status, and ethnicity were significantly associated with co-occurrence (Table 1). Seventy-five of the 100 children with co-occurrence were male and 25 were female.

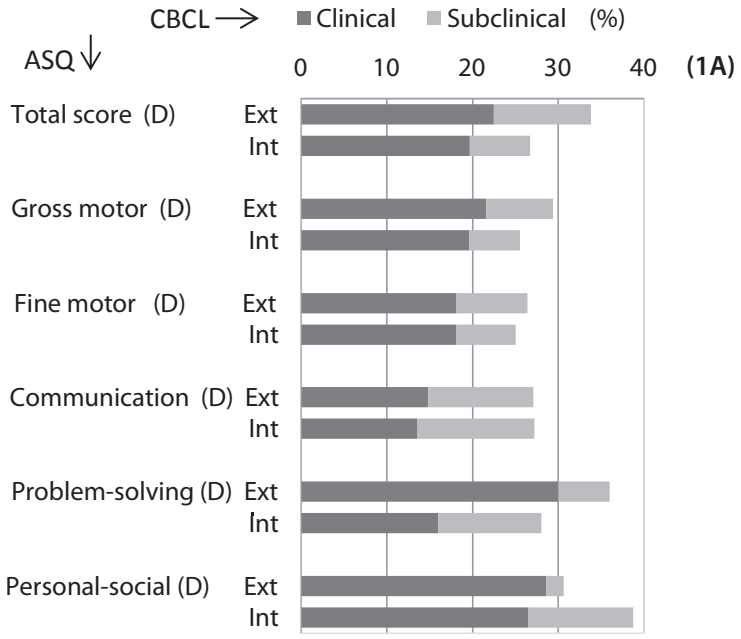
In Figure 1, we present prevalence rates of EBP in children with developmental delay. We assessed EBP (subclinical and clinical-range CBCL scores) separately for ASQ total problems and the ASQ domains gross motor, fine motor, communication, problem-solving and personal-social skills. Overall, MLP children with developmental delay (Figure 1A) had higher rates of EBP than MLP children without developmental delay (Figure 1B) and full-term children with and without developmental delay (Figure 1C and 1D), particularly with respect to clinical-range problems, i.e. a CBCL score above the 90th percentile. In MLP children with an abnormal ASQ total problems-score, rates of abnormal CBCL scores were more prevalent than in full-term children, particularly regarding

Table 1 Baseline characteristics of study participants with and without co-occurrence[a]

	Co-occurrence N=100	No co-occurrence N=1341	*P* value
Variables, mean (SD)			
Gestational age (weeks)	35.3 (SD 2.4)	36.1 (SD 2.9)	.004
Birth weight (grams)	2517 (SD 619)	2747 (SD 800)	.005
Age of child CBCL (months)[b]	45.0 (SD 1.7)	44.8 (SD 4.3)	.62
Age of child ASQ (months)[b]	45.0 (SD 1.3)	45.2 (SD 1.4)	.19
Variables, % (n)			
Gestational age (cohort)			.002
Fullterm	23.0 (23)	38.4 (515)	
Moderate to late preterm, total	77.0 (77)	61.6 (826)	
32 weeks	6.0 (6)	7.4 (99)	
33 weeks	18.0 (18)	12.0 (161)	
34 weeks	18.0 (18)	17.4 (233)	
35 weeks	35.0 (35)	24.8 (333)	
SGA[c]	11.0 (11)	8.6 (115)	.41
Male gender	75.0 (75)	52.6 (705)	<.001
Part of multiple	17.0 (17)	18.5 (249)	.50
One-parent family	8.1 (8/99)	5.6 (74/1333)	.30
Number of siblings			.09
0	12.0 (12)	16.8 (225)	
1	51.0 (51)	54.9 (736)	
2	24.0 (24)	21.4 (287)	
≥ 3	13.0 (13)	6.9 (93)	
Maternal age (years)			.003
< 25	16.0 (16)	6.8 (88/1301)	
25-34	66.0 (66)	73.4 (955/1301)	
> 34	18.0 (18)	19.8 (258/1301)	
Socioeconomic status[d]			.002
Low	25.0 (25)	17.2 (231)	
Medium	69.0 (69)	63.2 (847)	
High	6.0 (6)	19.6 (263)	
Maternal ethnicity			.002
Netherlands	87.0 (87)	95.2 (1262/1325)	
Europe	4.0 (4)	1.5 (20/1325)	
Non-European country	9.0 (9)	3.2 (43/1325)	

[a] Co-occurrence of developmental delay (ASQ total or domain score >2SD below mean) and emotional/behavioral
problems (CBCL score >84th percentile for total, internalizing or externalizing problems).
[b] Age at completing the CBCL and the ASQ, respectively.
[c] SGA, small for gestational age: birth weight below the 10th percentile of the Dutch Kloosterman growth charts.
[d] Socioeconomic status: composite measure of parental education, occupation, and family income (standardized
score with categories >1 SD below mean, mean +/- 1SD, and above mean +1SD.

externalizing problems: 33.8% (22.5% clinical range) vs. 23.8% (4.8% clinical range), respectively. Regarding the five ASQ domains, rates of (sub)clinical EBP varied from 25% to 39% in MLP children (Figure 1A). Delay in problem-solving skills frequently co-occurred with externalizing problems (36.0%, including 30.0% clinical range) and delay in personal-social skills with internalizing problems (38.7%, including 26.5% clinical range).



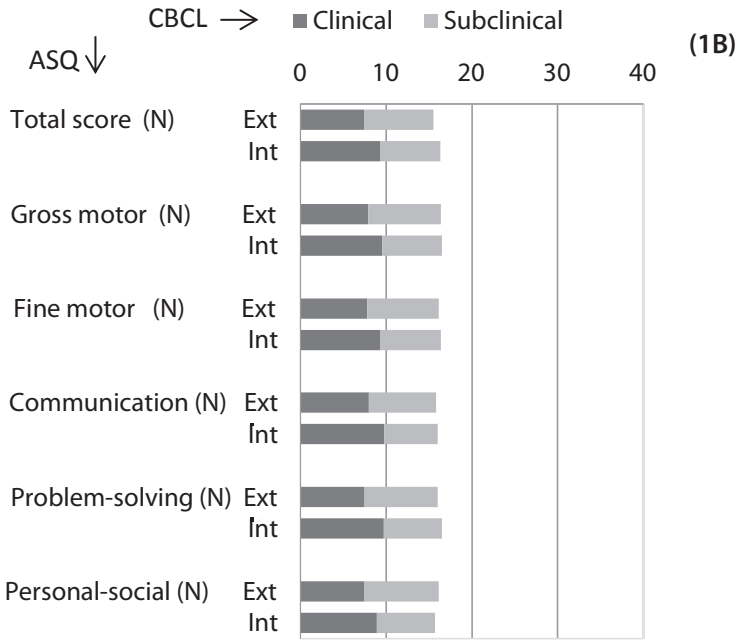
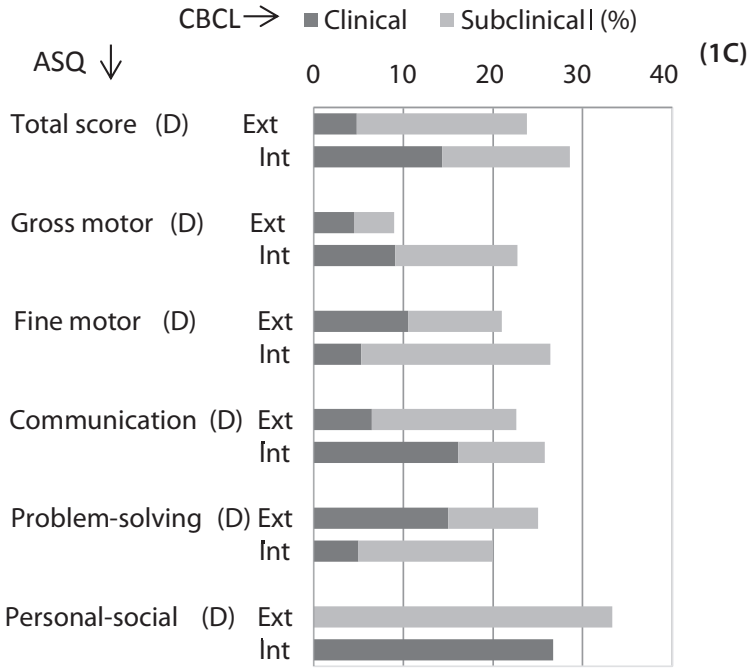


Figure 1 Rates of externalizing (Ext) and internalizing (Int) problems for the ASQ total score and for the five ASQ domains, (A) in moderate to late preterms with abnormal ASQ scores [i.e. developmental delay, *per domain*], (B) in moderate to late preterms with normal ASQ scores, (C) in fullterms with abnormal ASQ scores, and (D) in fullterms with normal ASQ scores.


CBCL→ Clinical Subclinical (%)
ASQ ↓
0 10 20 30 40
(1C)
Total score (D) Ext Int
Gross motor (D) Ext Int
Fine motor (D) Ext Int
Communication (D) Ext Int
Problem-solving (D) Ext Int
Personal-social (D) Ext Int

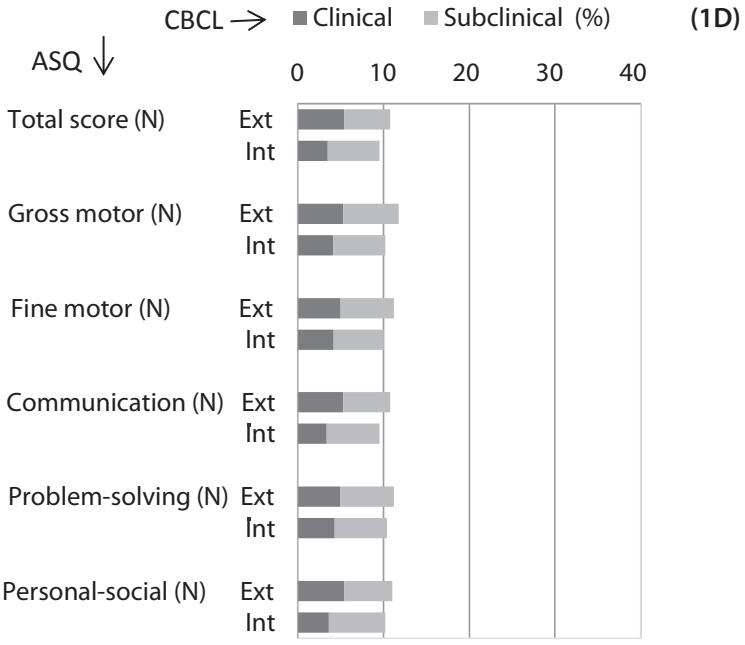

CBCL → Clinical Subclinical (%)
(1D)
ASQ ↓
0 10 20 30 40
Total score (N) Ext Int
Gross motor (N) Ext Int
Fine motor (N) Ext Int
Communication (N) Ext Int
Problem-solving (N) Ext Int
Personal-social (N) Ext Int

Table 2 shows that MLP children were more likely to have some type of developmental delay co-occurring with EBP than full-term children (unadjusted odds ratio (OR) 2.09, 95% confidence interval (CI) 1.29 to 3.37). Fewer girls than boys had developmental delay co-occurring with EBP, and the few girls with co-occurring problems were almost all MLP children (22 out of 25).

Table 2 Developmental delay co-occurring with emotional and behavioural problems in moderate to late preterm versus fullterm children: prevalence and odds ratios

	% (n/N)	OR (95% CI)	*P* value
Overall			
Fullterm	4.3 (23/538)	1	
MLP	8.5 (77/903)	2.09 (1.29 to 3.37)	0.003
Boys			
Fullterm	7.6 (20/264)	1	
MLP	10.7 (55/516)	1.46 (0.85 to 2.49)	0.169
Girls			
Fullterm	1.1 (3/274)	1	
MLP	5.7 (22/387)	5.45 (1.61 to 18.38)	0.006

MLP = moderate to late preterm; OR = odds ratio (unadjusted); CI = confidence interval

In multivariate logistic regression analyses (Table 3) we included potential confounders step-by-step. Adjustment for gender (Model 1) and socioeconomic status (Model 2) both mitigated the effect of moderate prematurity on co-occurrence. In the final multivariate model (Model 3), the risk of co-occurrence was nearly twice as high in MLP children compared to full-term children (OR 1.86, 95% CI 1.14-3.03). Male gender, low family socioeconomic status, and young maternal age were independent risk factors for co-occurrence in Model 3.

Table 3 Developmental delay co-occurring with emotional and behavioural problems: multivariate logistic regression analyses (*N*=1,441)

	OR (95% CI)	*P* value
Model 1		
MLP birth	1.96 (1.21 to 3.17)	0.006
Male gender	2.60 (1.63 to 4.14)	<0.001
Model 2		
MLP birth	1.85 (1.14 to 3.00)	0.013
Male gender	2.58 (1.61 to 4.13)	<0.001
Socioeconomic status[a]	1.48 (1.20 to 1.83)	<0.001
Model 3		
MLP birth	1.86 (1.14 to 3.03)	0.013
Male gender	2.49 (1.55 to 3.99)	<0.001
Socioeconomic status[a]	1.40 (1.12 to 1.74)	0.003
Maternal age, years		
25-34	1	
<25	2.13 (1.16 to 3.93)	0.015
>34	1.05 (0.60 to 1.83)	0.862
Maternal ethnicity		
Netherlands	1	
Europe	2.75 (0.90 to 8.41)	0.077
Non-European country	2.04 (0.92 to 4.53)	0.081

MLP = moderate to late preterm; OR = odds ratio; CI = confidence interval
[a] Per standard deviation decrease in socioeconomic status

DISCUSSION

This population-based study demonstrated that a quarter to a third of MLP children with developmental delay had co-occurring EBP at preschool age, as measured by the ASQ and CBCL. Particularly clinical-range externalizing problems often co-occurred with overall developmental delay in MLP children, compared to full-term children. After we adjusted for socioeconomic status, gender, maternal age, and ethnicity, the risk of developmental delay co-occurring with EBP remained significantly higher for MLP than for full-term children.

To the best of our knowledge, this is the first study to report on the co-occurrence of developmental delay and EBP in MLP children. Prior studies on co-occurrence were done in very preterm children, born at less than 32 weeks' of gestation.[18,19] In one study, 50% of five-year-old very preterm children had more than one developmental or behavioural disability, measured as the co-occurrence of cognitive, behavioural, neurological and/or motor problems.[19] In another study from the same research group, motor impairment at the age of five was more likely

to co-occur with conduct, emotional, or hyperactivity problems in very preterm than in full-term children, but the full-term comparison group was small.[18] In our study, 25% to 39% of MLP children had some form of developmental delay co-occurring with clinical or subclinical EBP, which seems to be lower than the rates found in very preterm children but higher than those in full-term children, suggesting that there is a gradient in degree of co-occurrence by gestational age.

In general populations, evidence on the co-occurrence of developmental and behavioural problems is more widely available. Nevertheless, to date studies among children of preschool age are limited.[30] Many studies showed that motor problems, such as motor control problems and developmental coordination disorder (DCD), often co-occur with attention problems and ADHD.[15-17,31] On average, 36% of children with DCD have clinical-range psychosocial problems[17] and specifically, scores on ADHD symptoms and social problems seem to be higher.[15-17] Furthermore, the combination of deficits in attention, motor control, and perception problems, also called DAMP, occurs in 1% to 8% of seven-year-old children,[32] suggesting a joint aetiology for this combination of problems. The boy-girl ratio having DAMP is quite similar to the 3:1 ratio that we found.[32] Although this finding may be incidental, it may also point at a joint aetiology for developmental delay co-occurring with EBP, affecting boys and girls in a different way.

A number of neurophysiological and psychosocial hypotheses have been proposed to explain why developmental delay and EBP frequently co-occur.[15,33] First, co-occurrence of developmental delay and EBP may be a consequence of aberrations in certain brain networks.[33,34] Children with multiple brain network aberrations may be more vulnerable to exogenous or endogenous disturbances, resulting in a higher risk of expressing both developmental and behavioural problems.[33,34] Neuroimaging studies support this hypothesis, showing that children with developmental and attention problems exhibit a reduced functional connectivity in specific brain regions.[20] The brain network aberration-hypothesis could also explain why MLP children were more likely than full-term children to have developmental and behavioural problems: MLP children lack three to eight weeks of intrauterine brain development, which increases the likelihood of disruptions in brain development.[35,36]

Second, differences in rates of co-occurring developmental delay and EBP may partly be explained by parenting style and parent-child interactions. In families with preterm children, for example, worries about the child's health may lead to an overprotective parenting style.[39] It is known that both developmental delay

and EBP are associated with heightened levels of distress in families, potentially leading to negative long-term effects on child development.[14,37] Furthermore, because of the bi-directional association between parenting style and behavioural problems in offspring,[38] an enduring downward spiral may ensue, and the risk of co-occurring neurodevelopmental problems may increase.

The findings of this study need to be considered in the context of some strengths and limitations. A major strength was the large community-based sample of MLP children, without selection of particular high-risk groups. Second, we had access to multiple sources of information. This enabled us to cross-check information from parents with retrospective medical files and discharge letters which strengthened the validity of our findings. The study also had limitations. First, a relatively small number of full-term children had co-occurring problems (23 out of 538 children). In particular this limited us in interpreting the rates of EBP per developmental domain for these full-terms. In addition, we used parental questionnaires to assess developmental delay and EBP instead of professional observations. Nevertheless, the added value of parental reports was apparent in the identification of psychosocial problems in PCH centers.[40] Lastly, we were unable to take into account all risk factors associated with developmental delay and EBP, such as parental psychopathology and early experiences of emotional neglect.[41] We recommend taking these factors into account in further research on co-occurring problems in preterm children.

Conclusions

We have demonstrated that 25% to 39% of MLP children with developmental delay also have EBP, indicating that increased awareness is warranted for EBP in MLP children with developmental delay. Further research is needed to determine whether early detection of co-occurrence of developmental and behavioural problems pays out in better long-term health,[13,42,43] especially for children who are at multiple risk, such as MLP children with low family socioeconomic status.[29] Our findings indicate that much can be gained by addressing the problems of this vulnerable group.

Acknowledgements

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Chapter 6

Risk of coronary heart disease in men with poor emotion regulation: a prospective study

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ABSTRACT

Objective Many psychosocial factors have been associated with coronary heart disease (CHD), such as hostility, anger, and depression. We tested the hypothesis that these factors may have fundaments in emotion regulation capacities. Therefore, our aim was to determine whether poor emotion regulation directly predicted long-term risk of CHD.

Methods This nationwide study comprises a population of 46,393 men who were conscripted for compulsory military service in Sweden, in 1969/1970. Psychologists assessed emotion regulation at conscription (age 18-20 years), in a 20-30 minutes-long semi-structured interview about controlling emotions during childhood. CHD was defined as a first fatal or nonfatal event. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for poor and adequate versus good emotion regulation.

Results After 38 years of follow-up (1971 until 2009), 2,456 incident cases of CHD had occurred. Poor emotion regulation increased the risk of CHD (HR 1.31, 95% CI 1.18-1.45), adjusting for childhood socioeconomic position, anxiety, depression, and parental history of CHD. Full adjustment for lifestyle-associated factors, e.g. smoking and BMI, attenuated the HR to 1.08 (95% CI 0.97 to 1.21). In stratified analyses, the fully adjusted HR for poor emotion regulation remained increased among men with a parental history of CHD (HR 1.49, 95% CI 1.11 to 2.01).

Conclusions In the overall study population, poor emotion regulation had no direct effect on CHD beyond lifestyle-associated factors. Specifically in men with a parental history of CHD, poor emotion regulation in adolescence directly predicted long-term CHD risk.

INTRODUCTION

Many psychosocial factors have been associated with coronary heart disease (CHD), but disease pathways remain uncertain.[1-3] Research on the relation between psychosocial factors and CHD gained attention after Type A personality had been associated with a higher occurrence of CHD in 1959.[4] Type A personality was characterized as 'manifesting an intense, sustained drive for achievement and as being continually involved in competition and deadlines, both at work and in avocations'.[4] Subsequently, also other psychosocial factors have been linked with CHD, such as hostility and anger,[5] anxiety, depression, social isolation, and chronic psychological stress.[6-8]

In order to explain associations between psychosocial factors and CHD, several biological and behavioral mechanisms have been proposed, from inflammatory processes to lack of exercise and other lifestyle-associated factors.[6,9] Recently, some researchers have investigated whether poor emotion regulation could be associated with CHD.[3,10,11] Emotion regulation is an important predictor of depressive symptoms[12] and of distress over the life course.[13] It is defined as the capacity to effectively use and control emotions in relationships and across a range of emotional events[14,15] and has its foundations in early childhood, a period characterized by rapid cognitive and social-emotional development.[14,16]

Emotion regulation may be a fundamental factor contributing to the pathophysiology of CHD, in that it may influence the response to emotional events and psychological stress, covering adverse features of mental disorders and personality characteristics.[8,13,15,17] The relation between anger outbursts and CHD, for example, may have its fundaments in emotion regulation.[18] To date, however, very few studies have addressed whether poor emotion regulation has a direct and prospective association with CHD, and the level of evidence is limited.[3,10,11] Therefore, the aim of this study was to determine whether poor emotion regulation in late adolescence directly predicted subsequent long-term risk of CHD, independent of lifestyle-associated factors.

METHODS

Study population

This study is based on data from the nationwide survey of Swedish males who were conscripted for compulsory military service in 1969/1970, at age 18 to 20 years. The procedures and variables of the nationwide survey have been described previously.[19,20] Of all men conscripted, 5.5% were born in 1949, 17.8% in 1950, and 76.6% in 1951. Of the Swedish male population only 2-3% was exempted from conscription, in most cases due to severe handicaps or congenital disorders. All men underwent a two-day screening procedure, including extensive health examination at one of seven regional conscription centers in Sweden. Furthermore, the conscripts had to complete two extensive questionnaires: one about social and behavioral factors, and another about substance use. Ethical approval was granted by the Research Ethics Committee of the Karolinska Institutet, Stockholm. Due to the character of the database, it was impossible to trace persons and ask for informed consent. In an early stage, therefore, this was specifically mentioned in several applications to the Karolinska Institutet Ethical Review Board. The Board decided to waive the normal requirement for informed consent, since the database exists solely of anonymized record linkage data.

Assessment of emotion regulation

Trained psychologists were instructed to assess specific dimensions of a broader concept called 'mental functioning', including the emotional capacities 'social maturity', 'mental energy', and 'emotional control'.[21] They did this by means of a semi-structured interview which lasted 20 to 30 minutes per conscript. Below we describe how emotional control was assessed. For detailed information on other dimensions of mental functioning we refer to a recent article on conscript data.[21]

Emotional control was measured as the situational-dependent regulation of emotions, which is a fundamental aspect of the concept emotion regulation.[22] The psychologists were instructed to ask the conscripts how they emotionally responded to important situational-dependent events (e.g. in the family, at school or at work) which they had experienced in childhood and adolescence. Based on the answers of the conscripts, the psychologists rated emotional control on a five-point scale. Ratings 1 (very poor) and 2 (poor) were given to conscripts who seemed to lack the ability to regulate emotions effectively, having difficulties in controlling nervousness and aggression. Rating 3 (average) was given to conscripts who had

adequate emotion regulation capacity, not having particularly negative or positive deviations. Ratings 4 (good) and 5 (very good) were given to individuals who appeared to respond calmly and purposefully, with good control of nervousness and aggression. The inter-rater reliability among interviewing psychologists was tested a few years after conscription, on the basis of 30 tape-recorded interviews scored by 30 psychologists, and was rated as 'very high' (r=0.86) for the overall assessment of mental functioning.[23,24] Prevalence rates for ratings 1 to 5 were 6.1%, 23.9%, 40.3%, 24.1%, and 5.6%, respectively. For the analyses, we merged the five ratings into three categories of emotion regulation, a) poor, i.e. rating 1 to 2; b) adequate, i.e. rating 3; and c) good, i.e. rating 4 to 5.

Assessment of CHD

Participants were followed-up for a first event of fatal or nonfatal CHD from 1971 until 2009. At the end of follow-up participants were 58 to 60 years of age. CHD was defined as acute myocardial infarction, acute and sub-acute forms of ischemic heart disease, chronic ischemic heart disease, old myocardial infarction, angina pectoris, or asymptomatic ischemic heart disease (ICD-8 and ICD-9, 410-414 and ICD-10, I20-I25). Data was obtained by record linkage with the National Cause of Death Register and the National Hospital Discharge Register for 1971 to 2009. Both registers are administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden. In Sweden, the registration of hospital diagnoses started in 1964, but did not cover the whole country until January 1, 1987. A few cases of CHD could be missed, but it would have little effect because CHD events at those young ages are very rare.

Covariates

The conscription examination provided information on cardiorespiratory fitness,[25] resting systolic and diastolic blood pressures,[26] body weight and height,[27] and smoking habits.[27] Cardiorespiratory fitness was rated as a score from 1 to 9 on a bicycle ergonometric test. Blood pressure measurements were made after 5-10 minutes of rest on the first day of the conscript examination. We used body weight and height to calculate the body mass index (BMI, kg/m^2). In the questionnaire on substance use, participants were asked about their smoking habits (no smoking, 1-5 cigarettes, 6-10 cigarettes, 11-20 cigarettes, or > 20 cigarettes per day). Further, men who reported or presented any psychiatric symptoms in the psychologists' interview at conscription were seen by a psychiatrist. Diagnoses of anxiety and

depression at age 18 were recorded according to the ICD-8.[28] Information on years of education was obtained through linkage with the Longitudinal Database of Education, Income and Occupation, held by Statistics Sweden, for the year of 1990.

Data on parental history of CHD and childhood socioeconomic position was obtained via linking with parental records. The conscripts and parents were linked to each other through personal identification numbers by Statistics Sweden. Information on parental history of CHD mortality was obtained from the National Cause of Death Register for the years 1952-2003, administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden. Parental history of CHD was defined as death known from CHD at age 65 years or younger of the father or mother. Information on childhood socioeconomic position, i.e. parental occupation at age 9 to 11 of participants, was obtained from the National Population and Housing Census of 1960 (response rate 99%). Childhood socioeconomic position was classified based on the occupation of the father or other head of household and has previously been linked to CHD.[29] Because of missing values on covariates, the analyses were limited to 46 393 out of 49 321 participants.

Statistical analysis

First, we examined differences in characteristics of the conscripts with poor, adequate, and good emotion regulation. Chi-square tests and analysis of variance were used to compare proportions (categorical variables) and means (continuous variables), respectively, between the three groups. Next, we used Cox proportional-hazards regression models to examine the association between emotion regulation and incident CHD during follow-up. In the regression models BMI and blood pressure were entered as continuous variables. All other variables were entered as categorical variables. We computed hazard ratios (HRs) and 95% confidence intervals (CIs) for poor and adequate emotion regulation, with good emotion regulation serving as the reference category. We tested the proportionality of hazard using log-log curves, and there was no evidence against the proportionality assumption. In the first regression model, we adjusted for parental history of CHD, childhood socioeconomic position, anxiety, and depression. These factors were considered as confounders, as they may have caused emotion regulation deficits through genetic or other (common) pathophysiological mechanisms. We also conducted stratified analyses to assess whether the association of emotion

regulation and CHD was modified by the potential confounders of Model 1. In the second model, we further adjusted for lifestyle-associated factors, i.e. education, cardiorespiratory fitness, BMI, systolic blood pressure, diastolic blood pressure, and smoking, which were rather considered as mediators of the association between emotion regulation and CHD. We tested mediation effects of the lifestyle-associated factors by calculating the percent change in the regression coefficient relative to Model 1. Empiric 95% confidence intervals of the change in the coefficients were derived using 1000 bootstrapped datasets. Lastly, we restricted to hospital-verified diagnoses of acute myocardial infarctions as a sensitivity analysis to check if findings would be similar using an outcome with less chance of misclassification. Statistical analyses were performed in SPSS for Windows v. 22.0 (Chicago, Illinois).

RESULTS

Baseline characteristics by emotion regulation are shown in *Table 1*. Some characteristics of men with poor emotion regulation (30.0% of the men) were: smoking more than ten cigarettes a day, having a diagnosis of anxiety or depression, having lower cardiorespiratory fitness, and having fewer years of education. Parental history of CHD mortality was also more common in men with poor emotion regulation.

Of the 46 393 participants, 2456 (5.3%) experienced a first CHD event during follow-up. *Table 2* shows the HRs and 95% CIs for CHD during follow-up according to emotion regulation in the total population. Men with poor and adequate emotion regulation, respectively, had 1.39 and 1.12 times greater hazard than men with good emotion regulation. The point estimates were fairly robust in multivariable models including the covariates anxiety, depression, childhood socioeconomic position, and parental history of CHD (Model 1). After further adjustment for education, cardiorespiratory fitness, BMI, smoking, systolic blood pressure, and diastolic blood pressure (Model 2), the HR for poor emotion regulation was 1.08 (95% CI 0.97 to 1.21). Additional tests for mediation showed that smoking was the factor that most attenuated the association between poor emotion regulation and CHD, followed by education and cardiorespiratory fitness (Supplementary Table).

Table 1 Baseline characteristics of study participants by emotion regulation

Variable	Emotion regulation			*P* value
	Poor	Adequate	Good	
Total % (*n*)	30.0 (13915)	40.3 (18711)	29.7 (13767)	
Variables, % (n)				
Childhood socioeconomic position				<.001
High non-manual	36.2 (5035)	33.6 (6296)	29.2 (4016)	
Intermediate non-manual	22.0 (3066)	22.4 (4198)	19.7 (2715)	
Low non-manual	9.5 (1325)	9.8 (1836)	11.6 (1598)	
Skilled manual	14.9 (2073)	16.0 (2995)	20.3 (2793)	
Self-employed	4.5 (623)	4.5 (837)	6.9 (950)	
Unskilled manual	10.3 (1438)	11.7 (2180)	11.1 (1531)	
Reporting no occupation	2.6 (355)	2.0 (369)	1.2 (164)	
Education				<.001
9 years or less	31.3 (4361)	26.6 (4971)	17.4 (2393)	
10-11 years	29.7 (4139)	29.6 (5537)	24.7 (3402)	
12-13 years	13.4 (1860)	16.7 (3128)	18.8 (2589)	
14 years	9.5 (1319)	10.9 (2047)	15.0 (2065)	
15 years or more	11.9 (1657)	13.3 (2484)	21.1 (2899)	
Smoking, cigarettes per day				<.001
No smoking	34.4 (4793)	41.7 (7806)	48.7 (6705)	
1-5	9.6 (1341)	11.4 (2138)	12.6 (1732)	
6-10	19.5 (2711)	21.9 (4101)	20.6 (2833)	
11-20	29.2 (4065)	22.6 (4230)	17.0 (2341)	
> 20	7.2 (1005)	2.3 (436)	1.1 (156)	
Anxiety disorder	1.0 (145)	0.0 (5)	0.0 (1)	<.001
Depressive disorder	4.1 (567)	0.1 (15)	0.0 (2)	<.001
Parental history of CHD[a]	7.8 (1086)	7.0 (1309)	6.5 (890)	<.001
Variables, mean (SD)				
Cardiorespiratory fitness score	5.6 (1.8)	6.1 (1.8)	6.6 (1.8)	<.001
Body mass index, kg/m^2	20.9 (3.5)	20.9 (2.8)	21.2 (3.0)	<.001
Systolic blood pressure, mmHg	125.9 (12.0)	126.3 (11.8)	126.0 (11.7)	.002
Diastolic blood pressure, mmHg	73.1 (9.4)	72.9 (9.3)	72.5 (9.7)	<.001

[a] Parental history of fatal CHD before 65 years of age

Table 2 Hazard ratios (95% confidence intervals) for CHD during follow-up according to emotion regulation

Emotion regulation	Cases N (%)	Incidence rate[a]			
			Unadjusted	Model 1[b]	Model 2[c]
Poor	859 (6.2)	186	1.39 (1.25 - 1.54)	1.31 (1.18 - 1.45)	1.08 (0.97 - 1.21)
Adequate	959 (5.1)	138	1.12 (1.01 - 1.24)	1.08 (0.98 - 1.20)	0.98 (0.89 - 1.09)
Good	638 (4.6)	124	Reference	Reference	Reference

[a] Incidence rate expressed as number of events per 100 000 person-years.

[b] Model 1: adjustment for anxiety, depression, childhood socioeconomic position, and parental history of CHD.

[c] Model 2: further adjustment for education, cardiorespiratory fitness, BMI, smoking, systolic blood pressure, and diastolic blood pressure.

Stratified analyses for explanatory variables indicated effect modification by parental history of CHD: *P* values for interaction between poor emotion regulation and parental history of CHD were 0.043 (Model 1) and 0.037 (Model 2). Stratification by other variables did not indicate effect modification. Even after full adjustment for cardiovascular risk factors, the association between poor emotion regulation and CHD was more pronounced in participants with a parental history of CHD (HR 1.49, 95% CI 1.11-2.01) than in those without (HR 1.02, 95% CI 0.90-1.14), as shown in Model 2 of *Table 3*. This difference is illustrated in *Figure 1*, showing the cumulative rates of CHD stratified by parental history of CHD. The interaction between poor emotion regulation and parental history of CHD (i.e. CHD mortality before age 65) was not explained by the loss of a parent at a young age. After we had stratified by 'all-cause parental death apart from CHD' instead of by 'early parental death due to CHD', HRs were 1.33 (95% CI 1.00-1.76) and 1.04 (95% CI 0.78-1.39) for Model 1 and 2, respectively.

Sensitivity analyses, i.e. restriction to hospital-registered diagnoses of acute myocardial infarction, showed similar or higher HRs as in the main analyses. E.g. for Model 1, the HRs for poor compared to good emotion regulation were 1.79 (95% CI 1.23-2.59) and 1.26 (95% CI 1.08-1.47) in men with and without parental history of CHD, respectively.

Table 3 Hazard ratios (95% confidence intervals) for CHD during follow-up according to emotion regulation, stratified by parental history of CHD

	Positive parental history (*N*=3285)		**Negative parental history (*N*=43108)**	
Emotion regulation	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Poor	1.68 (1.27-2.22)[c]	1.49 (1.11-2.01)[c]	1.25 (1.12-1.40)	1.02 (0.90-1.14)
Adequate	1.23 (0.93-1.63)	1.17 (0.88-1.56)	1.06 (0.95-1.18)	0.95 (0.85-1.06)
Good	Reference	Reference	Reference	Reference

[a] Model 1: adjustment for anxiety, depression, and childhood socioeconomic position.
[b] Model 2: further adjustment for education, cardiorespiratory fitness, BMI, smoking, systolic blood pressure, and diastolic blood pressure.
[c] *P* values for interaction between poor emotion regulation and parental history of CHD were 0.043 (Model 1) and 0.037 (Model 2).

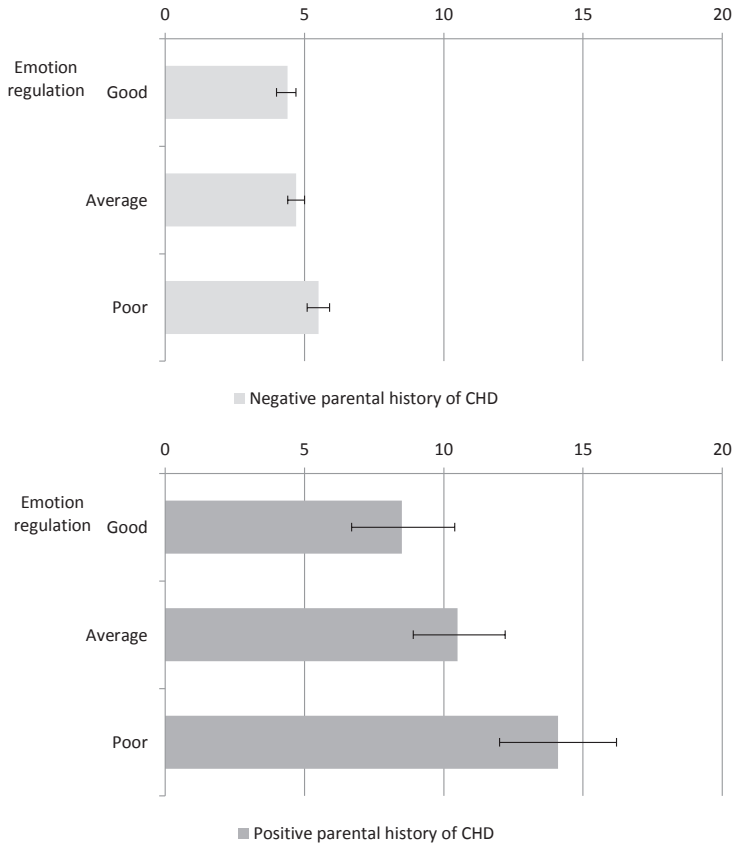

Figure 1 Cumulative incidence of CHD by level of emotion regulation capacity, in men with negative and positive parental history of CHD before age 65. The error bars depict 95% confidence intervals.

DISCUSSION

We found that poor emotion regulation in late adolescence was associated with an increased risk of CHD. This was more pronounced in participants with a parental history of CHD than in those without. In the total study population, adjustment for lifestyle-associated risk factors such as smoking, BMI, education, and blood pressure, largely attenuated the association between poor emotion regulation and CHD.

Our finding that poor emotion regulation was associated with an increased risk of CHD supports the evidence from some small prior studies, although these studies used alternative measures for emotion regulation. Two prospective cohort studies provided evidence for an inverse association between emotion regulation

and CHD,[3] and cardiovascular risk factors of CHD.[10] In the somewhat larger study, including 1122 men, higher levels of self-reported emotion regulation were associated with a decreased risk of CHD.[3] Results of the other study, among 415 adults, showed that higher levels of childhood attention regulation – measured as a specific form of self-regulation – increased the probability of having a favorable cardiovascular risk.[10] Separate later analyses on data of this study showed that emotion regulation deficits were not associated with higher cardiovascular disease risk.[11] Our study adds to the current evidence, as it provides greater statistical power, a more objective assessment of emotion regulation by psychologists, and little probability of reverse causation.

Poor emotion regulation may lead to CHD via two main pathways. First, having difficulties in regulating emotions may lead to health-compromising behaviors.[30] Our findings support this explanation because lifestyle-associated factors seemed to explain much of the link between poor emotion regulation and CHD in the majority of the men. In the causal pathway, we consider lifestyle-associated factors as mediators rather than confounders because they are more likely to be consequences of poor emotion regulation than causes of it, e.g. in the case of smoking.[31] Also in the association between depression and CHD, lifestyle-associated factors seem to have a mediating role.[32] Treating lifestyle-associated risk factors as confounders may even lead to underestimation of the potential effect of psychosocial factors.[7, 8]

Second, chronic psychological stress may explain the association between poor emotion regulation and CHD, as emotion regulation may (partly) reflect one's ability to respond to psychological stress. Low ability to control stressful situations may result in chronically high stress levels, which leads to activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system,[8] ultimately resulting in higher blood pressure and acceleration of the atherosclerotic process.[8,33] Psychological stress due to poor emotion regulation can also be considered as a dysfunctional feature of certain personality traits and mental disorders. Several personality traits, such as neuroticism,[34] adjustment disorders,[34] and hostility and anger,[18,35] have been associated with unhealthy responses to daily psychological stressors and higher cardiovascular risk.[8,17,36] Chronic psychological stress itself often goes along with depression and anxiety, which have independently been associated with cardiovascular diseases.[8,37] Genetic factors may be involved here: CHD patients who are carrier of the s allele of 5-HTTLPR are more vulnerable to depression and perceived stress.[38] Our findings may be interpreted

as supporting the psychological stress-pathway, because emotion regulation was inversely associated with CHD, independent of lifestyle-associated risk factors, in men with a parental history of CHD.

Our finding of a stronger association between poor emotion regulation and CHD in men with a parental history of CHD implies that familial factors might be involved. However, this was an unexpected finding, and we can only speculate about its background. One possibility is that poor emotion regulation increases the impact of psychological stress in families with high susceptibility to stress. Indeed, evidence from prior studies indicates that the combination of specific genes with psychological stress increases the risk of CHD.[1,38,39] Furthermore, twin studies have shown a significant genetic contribution to individual differences in cardiovascular reactivity to psychological stress.[40] Further research is needed to identify and specify the link of familial CHD risk with poor emotion regulation. In this context, it is also interesting which mediation pathways are important in the association between poor emotion regulation and CHD. In this study, the pathway between emotion regulation and development of CHD appeared to be mediated by smoking, education, and cardiorespiratory fitness but not by BMI and blood pressure. Therefore, future studies should focus on disentangling the specific pathways that link poor emotion regulation with a higher occurrence of CHD.

We believe that this study has major strengths. First, the large cohort provided an ample statistical power to investigate the research question. Second, there was little risk of selection bias since very few men were exempted from conscription examinations, and there was no self-selection because military service was mandatory in Sweden around 1969/1970. In addition, CHD events were followed prospectively via registers, providing high quality of follow-up and no loss to follow-up, except for the rare case of emigrating from Sweden.[41] Conscript data was linked with data from National registers on hospitalization and cause of death. Lastly, a unique characteristic of this study is that psychologists assessed emotion regulation capacity at age 18 to 20, which greatly reduced the probability of reverse causation. The latter was a weakness of previous studies in which emotion regulation had been measured at middle age or even older ages.

Our study also has limitations. Study participants were exclusively Swedish men, which limits generalizability. The findings also do not necessarily apply to CHD events at older ages because participants were about age 60 at the end of follow-up. Furthermore, the effect of emotion regulation as measured at conscription might have been diluted over the long follow-up time, although

it is unknown yet how emotion regulation relates to (healthy) ageing.[22] Some lifestyle-associated factors, i.e. BMI, cardiorespiratory fitness, smoking, and blood pressure, were also likely to change during follow-up. However, changes in these risk factors later on are consequences rather than causes of our exposure, which may have led to an underestimation of the real effects. We also consider it a limitation that the assessment of specific dimensions of the conscripts' mental functioning took place in 1969/1970, which limited us in interpreting what exactly the psychologists measured in relation to the current theory on emotion regulation. In this study, the term emotion regulation was used as a measure for the conscripts' emotional responses on important situational-dependent events in childhood and adolescence. This description fits with core features of emotion regulation, but it may also fit to related constructs, such as coping ability and mood regulation. However, it is yet uncertain how these constructs are related to each other.[22] Finally, we only have information on reliability tests for the overall assessment of 'mental functioning' – which was found to be 'very high' – and not for the specific dimension of emotional control.

Summarizing, in the overall study population poor emotion regulation had no direct effect on CHD beyond lifestyle-associated factors. However, the same thing cannot be concluded for subjects with a parental history of early CHD, as poor emotion regulation had a moderately strong association with CHD in this high-risk group, also after adjustments. If other studies would confirm these findings, they may provide new possibilities for primary and secondary prevention of CHD in high-risk groups. Many individuals are exposed to difficulties in emotion regulation (30% in this study), and a variety of psychological interventions, including emotion regulation interventions and coping with stress exposure, have shown to improve health in clinical populations.[42-45] However, intervention studies should also include non-clinical, high-risk populations because very little is known about the effectiveness of psychological interventions in healthy, but at risk populations.

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Supplementary Table

Mediation effects of lifestyle-associated factors on the association between emotion regulation and CHD

	Overall (*N*=46393)		Positive parental history (*N*=3285)	
Lifestyle factor	β	% β change (95% CI) [b]	β	% β change (95% CI)[b]
Reference[a]	0.27	Ref	0.52	Ref
+Education	0.19	-29.6 (-22.9, -53.3)	0.48	-7.7 (-2.7, -20.4)
+Cardiorespiratory fitness	0.23	-14.8 (-12.6, -27.5)	0.48	-7.7 (-6.3, -12.3)
+Body mass index	0.28	+3.7 (+1.1, +7.8)	0.53	+1.9 (+1.3, +0.6)
+Smoking	0.14	-48.1 (-35.0, -80.2)	0.42	-19.2 (-13.7, -38.7)
+Systolic blood pressure	0.27	=	0.52	=
+Diastolic blood pressure	0.27	=	0.52	=

[a] Model 1: adjustment for anxiety, depression, childhood socioeconomic position (and parental history of CHD in overall study population).

[b] Regression coefficients (β) were derived from Cox regression analyses. Empiric 95% confidence intervals of the change in the coefficients were derived using 1000 bootstrapped datasets.

Chapter 7

General discussion

The main aim of this thesis was to determine the associations between moderate prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective. This chapter includes an overview of the main findings and a discussion of the findings in the light of the relevant literature. Finally, implications for clinical practice, policy, and research are given.

MAIN FINDINGS

Research question 1 (Chapter 2): Are moderate prematurity and low SES independently associated with developmental delay at pre-school age, or do they have joint effects?

We hypothesized that differences in SES could partially explain the association of moderate prematurity with developmental delay. Findings from multivariate logistic regression analyses showed that this was not the case: moderate prematurity and low SES had separate, multiplicative effects on developmental delay. Prevalence rates for overall developmental delay were 12.5% in MP children with low SES, compared to 2.8% in full-term children with high SES. In particular, the developmental domains fine motor skills, communication, and personal-social skills were affected in MP children. Neither moderate prematurity nor low SES was associated with delay in gross motor skills, and finally, low SES mainly explained the occurrence of problem-solving skills at the age of four years.

Research question 2 (Chapter 3): What is the prevalence of behavioural and emotional problems in four-year-old, moderately preterm-born children, compared to the prevalence in full-term children?

We found that the rates of behavioural and emotional problems were higher in MP children than in full-term children. MP children had poorer mean scores on all CBCL syndrome scales, i.e. emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behaviour. They were also more likely to have scores in the clinical range, on total problems, externalizing problems, internalizing problems, and somatic complaints. Lastly, prevalence rates of behavioural and emotional problems differed by gender: overall the prevalence rates were higher among preterm-born boys and full-term boys, while being born moderately preterm affected girls more than boys.

Research question 3 (Chapter 4): Are moderate prematurity and low SES independently associated with behavioural and emotional problems at pre-school age, or do they have joint effects?

We hypothesized that low SES could explain why 8% to 10% of MP children struggle with behavioural and emotional problems. Therefore, our aim was to determine the separate and joint effects of moderate prematurity and low SES. We demonstrated that MP birth and low SES had separate, multiplicative effects on behavioural and emotional problems. This result did not confirm our hypothesis since we expected that low SES would partly explain the effects of moderate prematurity. In line with the gender differences shown in Chapter 3, girls were also more susceptible to the effects of low SES than boys. The difference between MP girls from low and from high SES families was great: 13.0% of the low SES girls had clinical-range problems, compared to an average of 4.9% in all girls participating in the study.

Research question 4 (Chapter 5): What is the prevalence of developmental delay co-occurring with emotional and behavioural problems in four-year-old, moderately preterm-born children compared to the prevalence in full-term controls?

In the total study population, 100 out of 1 441 children (6.9%) had some form of co-occurring developmental delay and emotional and behavioural problems. In the subgroup of MP children with developmental delay, on average 8%, rates of emotional and behavioural problems varied from 25% to 39% depending on the type of developmental delay. We also found that male gender, young maternal age, low SES, and non-Dutch ethnicity were significantly associated with co-occurrence. These factors were all included in the statistical analyses. The final statistical model showed a nearly twofold increase in the risk of co-occurrence in MP children compared to full-term children.

Research question 5 (Chapter 6): Does poor emotion regulation in 18-year-olds predict the risk of coronary heart disease?

Emotion regulation may be a fundamental competence contributing to the pathophysiology of coronary heart disease (CHD), in that it may influence the ability to cope with emotional events. We found that poor emotion regulation at the age of 18 was associated with a higher cumulative incidence of CHD, bridging a time span of nearly 40 years. Overall, the point estimates were fairly robust in multivariable models including childhood socioeconomic position, anxiety,

depression, and parental history of CHD mortality. Full adjustment for lifestyle-associated factors largely attenuated the increased risk, and tests for mediation showed that the association between poor emotion regulation and CHD in the majority of the population was mainly through smoking, education, and cardiorespiratory fitness. Unexpectedly, we found that the association between poor emotion regulation and CHD was more pronounced in participants with a parental history of CHD than in those without, showing that the effect of poor emotion regulation on CHD goes beyond lifestyle-associated factors.

DISCUSSION OF THE MAIN FINDINGS

Neurodevelopmental problems in MP children with low SES: some possible explanations

In Chapters 2 and 4 we found that moderate prematurity and low SES had separate effects on most developmental and behavioural outcomes. In other words, MP children are at risk of neurodevelopmental problems and low family SES further increases this risk. This finding coincides with other recent population-based studies: the effects of moderate prematurity seem to be robust, with low SES acting as an additional risk factor that contributes significantly to poorer neurodevelopmental outcomes.[1, 2]

Moderate prematurity and low SES may lead to neurodevelopmental problems via the following three pathways: 1) prenatal influences, 2) parental well-being and parental involvement during the pre-school years, and 3) disruptive effects of moderate prematurity and low SES on brain development. Many of the factors involved in these pathways have been linked to moderate prematurity as well as to low SES, suggesting common aetiological grounds.

Prenatal influences

Several prenatal factors, such as smoking, poor nutrition, and inadequate use of prenatal care, may lead to poorer neurodevelopmental outcomes in preterm-born and low SES children. These socioeconomically graded factors increase the risk of spontaneous preterm birth and other adverse pregnancy outcomes.[3, 4] We also know that antenatal maternal stress and anxiety contribute for approximately 15% to developmental and behavioural problems in offspring.[5] Psychological stress during pregnancy is a strong and consistent risk factor for preterm birth, and

low SES has been identified as one of the main determinants of maternal distress during pregnancy.[6, 7] The effects of maternal psychological stress on child health seem to persist long after birth: antenatal maternal stress has been associated with emotional and behavioural problems in childhood[8] and with depression in adolescence.[9]

Parental well-being and involvement during the pre-school years

Neurodevelopmental problems may arise as a consequence of poor parental psychological well-being during the early pre-school years. Due to increased levels of stress, the quality of parenting and parent-child interactions decreases. Parents who experience psychological stress tend to be less attentive and less sensitive, or conversely, they tend to be overprotective.[10-13] Either extreme may increase the risk of emotional and behavioural problems in children.[14]

Preterm birth and low SES have both been identified as potential sources of stress for families.[10, 15, 16] Mothers of preterm children may experience more psychological stress due to concern about their children's health, which results in worrying, anxiety, and feeling depressed. Even mothers of children born late preterm experience more emotional distress than mothers of full-term children.[10] Moreover, low SES may increase feelings of distress among parents, for example, concern about how to meet the family's needs.[12] To stop young children from crying, parents exposed to high levels of SES-related stressors, such as unemployment and/or low income, also tend to resort to actions that could be qualified as child abuse.[13] At the same time, low SES parents often have limited resources for financial and emotional support and more difficulties in accessing healthcare services.[15] If parental psychological stress is not recognized and alleviated in time, the effects of psychosocial problems on offspring can be long-lasting, as illustrated by depressive symptoms in the long term.[9]

Disruptive effects of moderate prematurity and low SES on brain development

Moderate prematurity and low SES may have direct effects on brain development. At 32 weeks' gestation, the volume of the brain has reached only 60% of its volume at full-term gestation.[17] At three months of age, after a period of rapid brain growth, the infant's brain has already grown from one third to one half of adult brain volume.[18] The lack of three to eight weeks of intrauterine brain growth may have consequences for neurodevelopment. Indeed, some specific alterations in

microstructural and neural connectivity processes have been found in the brains of preterm children.[19] Given their developmental stage at birth, particularly MP and late preterm children particularly lack part of the intrauterine development of the limbic system and cerebellum, in which structural changes take place after 32 weeks of gestation. Therefore, lacking the last stage of intrauterine brain growth may later become manifest as difficulties in controlling complex motor or mental tasks.[20-22] Corresponding with this biological explanation, impairments of MP children mainly include fine motor skills, handwriting, coordination, and verbal fluency,[23-26] contrary to the much broader array of developmental problems, including gross motor problems, in very preterm children.

Findings from the field of neuroscience indicate that low SES affects brain development, in particular involving those brain structures that are relevant for language processing.[15] Our study supports this notion, since low SES affected communication skills, including language comprehension, more so than other developmental domains. We found that 12.5% of full-term children with low SES had delay in communication skills compared to 2% of full-term children with high SES (Chapter 2). Importantly, the adverse effects of low SES in childhood do not stand on their own: prenatal factors, parent-child interactions, cognitive stimulation, and stress are all candidate mediators for the effects of low SES on brain development.[15, 27, 28] For example, stress may mediate effects of low SES because it has been related directly to the altered functioning of several brain areas and regulation systems, including the limbic system, the cerebellum, and the hypothalamic-pituitary-adrenal axis.[27-29]

Influence of SES on specific developmental domains

Low family SES had a greater influence on certain cognitive skills than on other developmental domains. First, problem solving skills in MP and full-term children were largely explained by SES, which confirms findings from prior studies. In preterm children born after 30 weeks of gestation, low parental educational level largely explained poorer cognitive outcomes, instead of preterm birth itself.[30, 31] Other researchers have estimated that the intelligence quotient decreases with two points per week of decrease in gestational age,[32] but it is unclear whether this translates directly into delayed cognitive development and eventually lower educational attainment. The latter seems to depend on genetic and socioeconomic determinants rather than on the gestational age of the child,[33] pointing at the prominent role of low family SES in long-term neurocognitive performance, in

particular regarding executive functioning.[34] In summary, low SES is an important risk factor for delay in problem-solving skills, also in MP children.

We found intriguing, mixed effects of low SES and moderate prematurity on communication skills, implying that SES had less influence on these skills in MP children (Chapter 2). Across all SES levels, 8% to 10% of MP children had delay in communication skills, contrary to full-term children, in whom these rates increased markedly with decreasing SES (from 2% to 13%), as expected. One explanation for this finding may be that MP children with low SES had received more special care than full-term children with low SES, which may have diminished the adverse effects of low SES. This explanation is, however, refuted by the fact that MP children were generally not recognized as at risk of developmental delay before the LOLLIPOP study commenced.[35]

Behavioural and emotional problems in MP children with developmental delay

In comparison to full-term children, we found that MP children had higher rates of behavioural and emotional problems at pre-school age, which is consistent with findings from other studies.[36] Most children, however, will not develop these problems at an early age,[37] but some children are at high risk of developing such problems later on. Co-occurrence of developmental and behavioural problems is one of the predictors of persistent problems. Of the MP children with developmental delay, up to a third had some form of co-occurring developmental and behavioural problems, which is considerable. To the best of our knowledge, no prior studies on co-occurrence have been done on MP children, although it has been suggested previously that in these children motor coordination problems, such as clumsy, uncoordinated movements, occurred frequently in combination with inattention, hyperactivity, and impulsivity.[38]

A number of neurophysiologic and psychosocial hypotheses have been proposed to explain why developmental and behavioural problems frequently co-occur.[39, 40] These hypotheses are partly in line with the main pathways that we proposed in order to explain higher rates of neurodevelopmental problems in MP and low SES children, i.e. the degree of parental well-being and involvement in the pre-school years, and the disruptive effects of moderate prematurity and low SES on brain development. Below, we briefly discuss two hypotheses that have been proposed in prior studies, and which may offer explanations for the emergence of co-occurring problems.

First, adverse family factors in the pre-school years may strengthen the effects of developmental delay on behavioural problems. As such, heightened levels of parental stress and negative parent-child interactions influence developmental delay as well as behavioural and emotional problems.[41, 42] Due to the bi-directional relation between negative parenting and behavioural problems in children,[43] an enduring downward spiral may ensue, and the risk of developmental delay co-occurring with behavioural and emotional problems may increase.

Second, co-occurrence of developmental and behavioural problems may be a consequence of disruptions in brain networks.[40, 44] Children with specific brain network disruptions may be more vulnerable to exogenous or endogenous disturbances, resulting in a high risk of experiencing both developmental and behavioural problems. This hypothesis could explain why MP and late preterm-born children are more likely than full-term children to have co-occurring problems. Their lack of three to eight weeks of intrauterine brain development compared to full-term children may increase susceptibility to brain network disruptions.[21, 22]

Gender differences in behavioural and emotional outcomes

Gender is an important determinant in the assessment of behavioural and emotional problems. In general, boys are more likely to have externalizing problems and girls have more internalizing problems, which is similar in preterm children.[32, 45, 46] Our results confirm these general differences between boys and girls. However, in contrast to our expectations, MP boys did not differ in behavioural outcomes compared to full-term boys. By contrast, MP girls showed significantly more behavioural and emotional problems than their full-term peers, as reported in Chapters 3 to 5. Previous reports on such gender differences between MP and full-term children are scarce. One recent study on precursors of symptoms of attention deficit hyperactivity disorder in 5-year-old MP children reported similar outcomes: preterm girls showed significantly more inattentive behaviour, hyperactivity, and impulsivity than full-term girls and boys, as rated by mothers and teachers.[38] A significant interaction between gender and gestational age was also found, indicating a stronger association between preterm birth and behaviour problems in girls.[38]

In prior studies on MP children, a greater susceptibility of girls to moderate prematurity may have gone unnoticed because of insufficient sample sizes to perform stratified analyses. First of all, outcomes in MP girls have often been

compared with outcomes in MP boys, leaving out comparisons with full-term peers of the same gender. By doing so, the effects of gender were assessed instead of the gender-differential effects of moderate prematurity. Moreover, comparisons with other studies were limited because of variations in gestational age and age of assessment of developmental and behavioural outcomes.[38, 46, 47] For a better comparison with our findings, larger cohorts of pre-school aged MP children are needed.

We also found that particularly preterm girls with low SES had poorer scores on externalizing and internalizing problems than girls overall. The prevalence rate of elevated total problems was 14% in MP girls with low SES compared to 4% in girls overall (Chapter 4). This may indicate that each additional neonatal or childhood adversity may have a multiplicative effect on girls' emotions and behaviour. As such, low birth weight in combination with multiple socioeconomic adversities also has a greater effect on adolescent mental health than if only low birth weight were present.[48] Nearly 100% of low birth weight girls with three or more adversities had depressive symptoms in adolescence.[48] In summary, our findings are in agreement with the evidence that boys are more likely to have behavioural problems, but that girls, in particular, developed emotional and behavioural problems as a consequence of preterm birth and early socioeconomic adversity.

Explanations for gender differences

Previous research may provide some clues for explaining the gender differences we found. In the first place, gender differences in vulnerability to neonatal and social adversities may have their origins in foetal development. Evidence indicates that boys and girls have a different physiological response to increased levels of stress hormones.[49, 50] A higher level of cortisol in pregnancy, as measure of maternal stress, has only been associated with more affective problems in 7-year-old girls, accounting for the effects of maternal depression during follow-up.[49] Interestingly, the association between high maternal cortisol levels and affective problems was partly mediated by volume changes of the right-sided amygdala, a region of the brain involved in emotional functioning.[49]

Second, girls go through a more rapid process of cognitive and emotional development in the pre-school years than boys, and this may increase their vulnerability to emotional events and social-environmental adversities that influence normal development,[51] such as lack of maternal warmth following

complications at birth. This hypothesis is supported by evidence showing that early experiences of stressful events, such as being bullied or the loss of a family member, have a greater impact on the mental health of girls than of boys throughout childhood, adolescence, and adulthood.[52, 53]

Furthermore, cognitive perception of life adversities differs by gender. In boys and girls, cognitive errors, for example, overgeneralization and catastrophizing, influence emotion and behaviour in a different way. In boys, cognitive errors mediate the association between life adversity and hyperactivity while in girls they mediate the association between life adversity and peer and emotional problems.[54] It is unclear, however, to what extent such mechanisms have an impact at pre-school age, considering the early stage of cognitive development.

Poor emotional functioning and the risk of coronary heart disease

Throughout life, indicators of poor emotional health have been associated with an increased risk of CHD and its metabolic precursors, including early life adversities,[55] chronic psychological stress,[56] mood disorders, and social isolation.[57, 58] In Chapter 6, we provide evidence that the emotion regulation capacities of young people are not only associated with affective disorders, but also with CHD. This association was largely mediated through heavy smoking, poor cardiovascular fitness, and lower educational attainment in adulthood. Similarly, in prior research, lifestyle-associated factors were found to mediate the association between depression and CHD.[59] Because of this link with lifestyle, improvement of emotion regulation skills may provide possibilities for the prevention of CHD, even in children. For example, 13-year-old teenagers with poor emotion regulation skills were more likely to consume junk food and to have sedentary lifestyles than peers with fair or good emotion regulation skills.[60]

In men with a parental history of CHD, we found an association between poor emotion regulation and CHD beyond effects of lifestyle and education. This was an unexpected finding, which generated some thoughts regarding possible explanations. First, the association could partly be explained by the impact of parental mortality due to CHD. Conscript data were linked to data on CHD mortality of the conscripts' parents, i.e. parental mortality before the age of 60 years. This meant that the conscripts were relatively young when one of their parents died. Therefore, the impact of early parental death may have caused mental and physical dysregulation that could eventually predispose to CHD. However, additional analyses for all-cause mortality, not due to CHD, did not explain the

association between poor emotion regulation and CHD risk. Second, the men with a familial risk of CHD might have had greater cardiovascular reactivity in response to emotionally charged events. Evidence from prior studies showed that individual differences in cardiovascular reactivity in response to psychological stress may have its origins in genetics.[61-63] This theory may also have links with certain personality traits and mental disorders that predispose to a higher risk of CHD. For example, neuroticism, adjustment disorders, hostility, and anger have been associated with unhealthy responses to daily psychological stressors and higher risk of cardiovascular disease.[58, 64, 65]

Developmental origins of emotional functioning

The foundations for long-term emotional health are laid in the prenatal period and early postnatal years, which are characterized by rapid cognitive and social-emotional development.[66] Therefore, the prenatal period and the early postnatal years are the most plastic and sensitive periods of life. This also implies a high vulnerability to early adverse environments.[67] It is clear that experiences of early life adversity affect social-emotional functioning, but the exact mechanisms and links with long-term health problems are unclear. Emotion regulation capacity may be involved here, since it may function as a buffer for harmful effects of early adverse events and environments.[15] For example, low SES children are more likely to have difficulties in emotion regulation, which hinders them in adequately responding on adverse events.[66] This calls for further research.

Early adversities may also increase vulnerability in some individuals and promote resilience in others. One explanation for this finding is that coping with adverse experiences effectively has the function of preparing a child for similar challenges in adulthood. [68] This may, however, only hold true if the child is capable of managing the challenges confronting him or her later on in life. Individuals who did not develop mental health problems after maltreatment in childhood were characterized by a higher number of protective factors, involving parental care, quality of relationships, and personality characteristics.[69] In these cases, it is the sum of adversities and protective factors that determines health outcomes after experiencing early life adversity.[48, 69] This fits with the evidence that cumulative experiences throughout life of socioeconomic and other disadvantages predict higher levels of cardiovascular and metabolic biomarkers.[70, 71]

METHODOLOGICAL CONSIDERATIONS

The LOLLIPOP study

LOLLIPOP is one of the largest community-based cohort studies on MP and late preterm-born children. Moreover, unlike many other cohorts, LOLLIPOP comprises a control group of full-term children who were sampled from the same preventive child healthcare (PCH) centres and who were in the same age-range as the preterm children. Children born between 36^0 to 36^6 weeks' gestation were not included since the main focus of the LOLLIPOP study was on outcomes of children born at 32^0-35^6 weeks' gestation. The effect of not including these children is likely to be small because many MP children were born at 34 and 35 weeks' of gestation, relative to 32 and 33 weeks' of gestation. Numbers of MP children increased for every week of gestation, reflecting the community-based character of the cohort. The sample size of LOLLIPOP was based on numbers in order to compile growth curves for Dutch preterm children, which asked for a large number of children.

Parents could choose between joining the full study, which included follow-up measurements, or only the 'growth curves' part of the study. As a consequence, the number of participants joining the follow-up part was lower. Among the non-participating children low SES was more common ($P<0.001$), which may have influenced our results. However, we think that the effects of SES would then have been an underestimation of the real effects. Gender and SGA did not differ significantly between participating and non-participating children.

For the purpose of this thesis only data from the first measurement were used, i.e. when the children were nearly four years old. This measurement was planned as part of the scheduled PCH visit of the children, resulting in high responses (up to 95%) on the study questionnaires. Since the PCH doctors and nurses were very much involved in the study, they actively reminded the parents to fill in the questionnaires. Moreover, population coverage was high because in the Netherlands around 95% to 97% of children visit PCH centres regularly from birth up to four years of age.

Measurement of SES

We chose to use a composite measure of SES rather than single SES indicators, in order to fully account for effects that can be attributed to socioeconomic conditions.[72, 73] We computed the composite score on the basis of five indicators: educational level of the mother, educational level of the father, the family income,

occupational level of the mother, and occupational level of the father. All five indicators were available for the majority of the participants. For some participants, however, data on one of the indicators was missing, in particular family income or the occupational level of the mother. The composite SES was measured using the available indicators. Since data on educational level of both parents was most complete, it is likely that these two indicators weighed somewhat heavier in the overall effect of SES than the other indicators.

Data on SES indicators were collected at different points in time. In a general questionnaire, parents were asked to fill in their highest completed educational level and the net monthly family income shortly before the scheduled PCH visit at four years of age. Data on occupational level, however, were collected retrospectively from the medical birth registers kept by the PCH centres. It is possible that the occupational level of the parents had changed between birth and four years later, for example, due to losing a job or obtaining a higher position. In this way, changes in occupational level could have led to positive or negative deviations regarding the effect on neurodevelopmental problems. For the same reason, the family income when the child was four years old may not fully represent the level of income from birth up to four years of age. It is likely that the composite SES gives a better impression of the SES from birth up to four years than each of the indicators alone.

Assessment of neurodevelopmental outcomes

We used parental questionnaires to assess developmental delay and behavioural and emotional problems. Parental reports have proven to be valid when it comes to signalling psychosocial problems in preventive child healthcare.[74] Nevertheless, additional testing by medical specialists or psychologists would have had added value, in the sense of providing a professional view on developmental and behavioural problems of the children in the LOLLIPOP study.

Using the ASQ as a screening instrument for measuring developmental delay has both advantages and disadvantages. The ASQ is a reliable and valid questionnaire for developmental screening, also in preterm children.[75-77] Practical advantages are that the ASQ is cheap and, generally, completed quickly. Most parents consider the questionnaire easy to fill in[78] and 97% can do so without the help of others.[79] Nevertheless, in the LOLLIPOP study not all ASQ domain scores were completely filled in by all the parents, which indicates that some parents may have had difficulties in comprehending the questions.[80] For example, the 25 (9.9%) of the low SES mothers who originated from non-European countries may have

had some trouble filling in the ASQ. Nevertheless, the effects on study outcomes were likely to be small, given the relatively small number of this group.

We assessed behavioural and emotional problems at the age of four using the CBCL. This questionnaire has good psychometric properties, is widely used in research and clinical settings, and is easily filled in by parents.[81] Some psychometric properties, for example, are the high test-retest reliability (r=0.85) and good predictive validity, with a correlation of 0.64 for the total problems score over a period of six years.[81] Most scores on the CBCL syndrome scales at pre-school age significantly predict higher CBCL scores at school age, with sometimes even better correlations over a longer time span.[81] Pre-school scores on the withdrawn syndrome scale, for example, correlate better with outcomes at the age of nine than at younger ages. Therefore, pre-school CBCL scores seem to reflect underlying problems that predict long-term psychosocial functioning.[81] From other studies we know that behavioural and emotional problems in children tend to persist into adolescence and even into adulthood.[82-84]

Clinical meaning of statistical significance and interaction

In the studies reported on in this thesis, we found statistically significant associations of gestational age and SES with developmental and behavioural outcomes. Statistical significance, however, is not always equal to clinical significance. For measuring clinical significance, effect size is the appropriate measure. By way of example, we measured the effect sizes of associations between moderate prematurity and behavioural and emotional problems, a measure which is relevant for clinicians taking care of children who have elevated CBCL scores. The effect sizes for elevated total, externalizing, and internalizing problems were 0.34, 0.27, and 0.50, respectively, meaning small (0.34 and 0.27) to moderate effects (0.50). This means that the threshold to initiate individual treatment for internalizing problems was reached. When looking at population level, the effects of all outcomes are rather important, given the prevalence of moderate preterm birth, and imply a major global burden of disease.

To determine the effect of SES on the association between moderate prematurity and neurodevelopmental problems, we measured statistical interaction between moderate prematurity and low SES. In logistic models, we found that SES did not interact with moderate prematurity with regard to most neurodevelopmental outcomes. This meant that the effects of SES and gestational age were multiplicative, as is the case for any logistic model without significant interactions. This absence

of statistical interaction in logistic models implies that having both risk factors increases the risk of neurodevelopmental problems considerably, relative to having only one of the risk factors. In other words, a multiplicative risk model applies.

The Swedish conscript study

The Swedish conscript study is a register-based study using data of over 45,000 men who were conscripted for military service in 1969 and 1970, and it covers a follow-up period of nearly 40 years. For this reason the study is well-suited to assess effects of mental and physical well-being on health during the course of the conscripts' lives. Therefore, the possibility of reverse causation is limited, enabling the researcher to disentangle cause and effect. On the other hand, long time spans between exposure and outcomes may either underestimate or overestimate the real effects. Emotion regulation was measured at conscription in 1969 and 1970 and follow-up for CHD occurred until 2009. The effect of emotion regulation might have been diluted over the long follow-up period, but it is unknown to which degree emotion regulation relates to healthy ageing.[66] Furthermore, lifestyle-associated factors, i.e. BMI, cardiorespiratory fitness, smoking, and blood pressure, were likely to change during follow-up. However, changes in these risk factors later on were consequences rather than causes of emotion regulation capacity, which may have led to an underestimation of the real effects.[57, 58]

As mentioned above, the assessment of the conscripts' mental functioning took place at conscription, which limited us in interpreting what the psychologists had exactly measured in relation to current theory on emotion regulation. The available information on the assessment of emotion regulation fits with core features of emotion regulation, although the described concept may also fit related constructs, such as coping and mood regulation. As yet it is unknown how the constructs of emotion regulation, coping ability, and mood regulation are interrelated.[66] The interrater reliability of the interviewing psychologists was tested a few years after conscription, on the basis of 30 tape-recorded interviews scored by 30 psychologists, and was rated as 'very high' (r=0.86) for the overall assessment of mental functioning.[85, 86]

Lastly, the generalizability of study outcomes is limited, in the sense that only men participated in the study. As a consequence, our findings cannot be generalized to women. Furthermore, the findings do not necessarily apply to CHD events at older ages because participants were about 60 years of age at the end of follow-up. Besides the fact that participants consisted of Swedish men only, the probability

of selection bias was very limited since only 2% to 3% of the male population was exempted from conscription, in most cases due to severe handicaps or congenital disorders.

IMPLICATIONS

The findings of the studies reported on in this thesis provide new insights relevant to preventive healthcare. On the basis of these finding, we offer recommendations for clinical practice and policy in PCH and we put forward several suggestions for further research aimed at two dimensions: 1) disentangling the pathways that lead to neurodevelopmental problems, and 2) the role of emotion regulation in promoting and maintaining mental and physical health in the long term.

Implications for clinical practice and policy

The greater part of the findings in this thesis applies to clinical practice in Dutch PCH centres. From our results it follows that indicators of low family SES and signs of co-occurring problems could contribute to the efficient detection of early emerging developmental and psychosocial problems in MP children.

In 2013, the Dutch National Centre for Preventive Youth Healthcare published a guideline on the early identification of developmental and psychosocial problems in preterm and small-for-gestational-age children.[87] This guideline also aimed at early detection of developmental and health problems in MP children, but specific recommendations were lacking. The findings presented in this thesis will help to specify the guidelines for MP children, who comprise by far the largest group of preterm children with whom PCH professionals are confronted. In particular, refinement of the guideline is needed because most, i.e. approximately 80% to 90%, of MP children will have no significant developmental or psychosocial problems.[88] In other words, PCH professionals know which MP children would benefit most from interventions, and we believe that the findings presented here will contribute to understanding this.

First, we found that the combined biological and social risk of MP children with low SES translates into a substantial increased risk of neurodevelopmental problems. This implies that increased awareness is warranted for the relatively large group of MP children with low family SES. Preterm birth occurs more often in low SES families, but low SES was not an explanation for the association between

preterm birth and neurodevelopmental problems. In addition, we found that those children with low family SES were characterized by certain features such as being part of a single-parent family, having a mother younger than 25 years, and having a mother of non-European ethnicity. This fits with the current PCH guidelines that identify these features as risk factors for psychosocial problems.[87, 89]

Second, co-occurrence of developmental and behavioural problems needs more attention in MP children. PCH professionals should be aware of the high probability of co-occurring behavioural and emotional problems if MP children have delays in one or more developmental domains. In particular, the combination of developmental delay with externalizing problems occurred frequently in MP children. Early identification of co-occurring developmental and behavioural problems is important because it predicts psychosocial problems at school age and beyond.[90-92]

Implications for further research

The findings presented in this thesis provide more insight into the pathways via which moderate prematurity and low SES lead to neurodevelopmental problems and via which emotion regulation may promote long-term health. Further research is needed to reveal the clinical implications of these findings.

Disentangling the pathways leading to neurodevelopmental problems

We proposed three pathways via which moderate prematurity and low SES may lead to neurodevelopmental problems: 1) prenatal influences, 2) parental well-being and parental involvement in the pre-school years, and 3) the disruptive effects of moderate prematurity and low SES on brain development. As we describe below, each of these pathways leads to ideas for further research.

1) Prenatal influences

Poorer mental and physical health during pregnancy increases the risk of mortality and morbidity in newborns. We proposed that antenatal maternal stress may initiate mechanisms leading to neurodevelopmental problems in preterm and low SES children due to the associations of antenatal maternal stress with all of these factors.[5, 7] A better understanding of these mechanisms may offer new possibilities for the prevention of preterm birth and neurodevelopmental problems. One suggestion is to investigate which part of the association between antenatal maternal stress and neurodevelopmental problems is through preterm

birth, while taking into account the effects of low family SES. Another idea would be to investigate to what extent higher levels of antenatal maternal stress lead to behaviour that is detrimental to the mother's health behaviour during pregnancy, such as smoking, malnutrition, and inadequate use of prenatal care, which in turn could cause neonatal morbidities and neurodevelopmental problems.

2) Parental well-being and parental involvement during the pre-school years

Preterm birth and low SES are sources of stress for families that may lead to the disruption of family interaction patterns. Parent-child and child-family interactions provide potential targets, i.e. risk and protective factors, for preventing neurodevelopmental problems in case a family is exposed to child-stressors, such as preterm birth, or SES-related stressors. Below, we briefly describe what is known on the effectiveness of interventions in preterm and low SES children and we offer suggestions for intervention studies based on the findings presented in this thesis.

Intervention studies on very preterm children have shown positive effects in the short term,[93] but long-term results are indifferent.[94, 95] The effectiveness of interventions in MP children are largely unknown. In one study, no effect was found of a 'mother-infant transaction program' regarding cognitive, motor, or behavioural development of MP children.[96] The authors suggested that the intervention might be more effective in those children at higher social or developmental risk.[96] In low SES families, interventions may better meet the needs of the family, for example, because of limited financial and social resources. Furthermore, children with multiple developmental delays may benefit more from interventions, given the lack of developmental resources and poor organizational capacities, i.e. executive functioning, meta-cognition, social cognition, motivation, and emotion regulation.[94, 97] Future intervention studies should investigate whether indeed MP children with low SES and/or with multiple developmental delays benefit more from interventions.

It is largely unknown whether interventions should be mainly directed to the competencies of the child, to well-being and parenting style of the parents, or to family resources. For example, interventions aimed at parenting style seem to be less effective in very preterm children regarding long-term developmental outcomes.[94, 95] Furthermore, nurse visits from birth up to two years of age especially benefited low SES children in terms of language, attention, and internalizing problems that were measured at 6 and 9 years of age.[98]

Lastly, the findings presented in this thesis imply that a gender-specific approach may be called for. Early detection and intervention may be more effective in girls, since they were more disadvantaged by the effects of moderate prematurity and low SES than boys. Because we were the first to assess these gender differences in behavioural and emotional outcomes after moderate prematurity, we call for confirmation of our findings and for further research to fully explain them.

3) Disruptive effects on brain development

Further research on brain development may improve our understanding of the pathophysiology of specific neurodevelopmental outcomes in MP and low SES children. For example, we have no adequate social-environmental explanation for the finding that effects of SES on communication skills were less pronounced in MP children. Insights from the field of neuroscience may provide an explanation for this finding. Questions also remain regarding the pathophysiology of behavioural problems in preterm-born children, such as: 1) Can the type of brain network aberrations explain the co-occurrence of specific developmental and behavioural problems? And 2) Do aberrations in the limbic system correspond with internalizing problems in preterm children, and in which way are gender differences involved?

The role of emotion regulation in maintaining mental and physical health

The findings presented in this thesis give rise to further research involving the role of emotion regulation in maintaining mental and physical health throughout life. To start with, little is known about the effectiveness of emotion regulation interventions in individuals who are at risk of CHD. In recent years, the role of emotion regulation has gained interest in health research,[66] but the possibilities for preventive child healthcare are largely unknown. Applicability of emotion regulation interventions are currently explored for a widening array of neurodevelopmental problems and disorders, such as attention deficit and hyperactivity disorder and co-occurring conditions,[99] and in various risk subgroups, including preterm-born and low SES children.[100-102]

Our findings also show that the association between emotion regulation and CHD was partly explained via smoking, cardiorespiratory fitness, and education. Because emotion regulation is a competence acquired mainly in early childhood, this implies that early investments in social-emotional competencies may pay off in health-promoting behaviours and lower risks of long-term health problems.

We recommend further research to disentangle the associations between emotion regulation, affective disorders, and CHD.

Additionally, it is unknown why the effect of emotion regulation goes beyond lifestyle-associated factors in individuals with a parental history of CHD. This finding may, for example, be explained by genetic factors which predispose an individual to stronger bodily responses to psychological stress. If at the same time the emotion regulation capacities are low as well, there is no safeguard against the harmful effects of stress.

CONCLUSION

In children and adolescents, biological risk factors and socioeconomic circumstances may threaten neurocognitive and social-emotional development, potentially affecting the foundations for life-long mental and physical health.

At the start of life, birth complications and socioeconomic disadvantages pose major risks for neonatal health and neurodevelopment. With the studies presented in this thesis, we demonstrated that moderate prematurity and low SES are separate risk factors that have multiplicative effects on neurodevelopmental problems in early childhood. Our findings imply that interventions should be directed at those MP children with the highest risk, since the majority of MP children will develop normally. In clinical practice, therefore, increased awareness is needed to identify those MP children with low SES and those with multiple developmental and behavioural problems. Furthermore, a gender-specific approach is called for since we found that girls were more vulnerable to the effects of moderate prematurity and low SES than boys.

Throughout life, emotion regulation skills acquired during childhood may help to promote the maintenance of mental and physical health. We found that young people's emotion regulation capacities predicted CHD across a lifespan of 40 years, which was partly explained by higher rates of unhealthy lifestyles among those individuals with poor emotion regulation capacities. Moreover, emotion regulation affected the risk of CHD beyond lifestyle-associated factors, specifically in men with a high familial risk of CHD.

In summary, moderate prematurity and low SES increase the risk of pre-school neurodevelopmental problems, potentially affecting the foundations of mental and physical health, and from a life course perspective, social-emotional competencies that are acquired in early childhood may promote long-term health.

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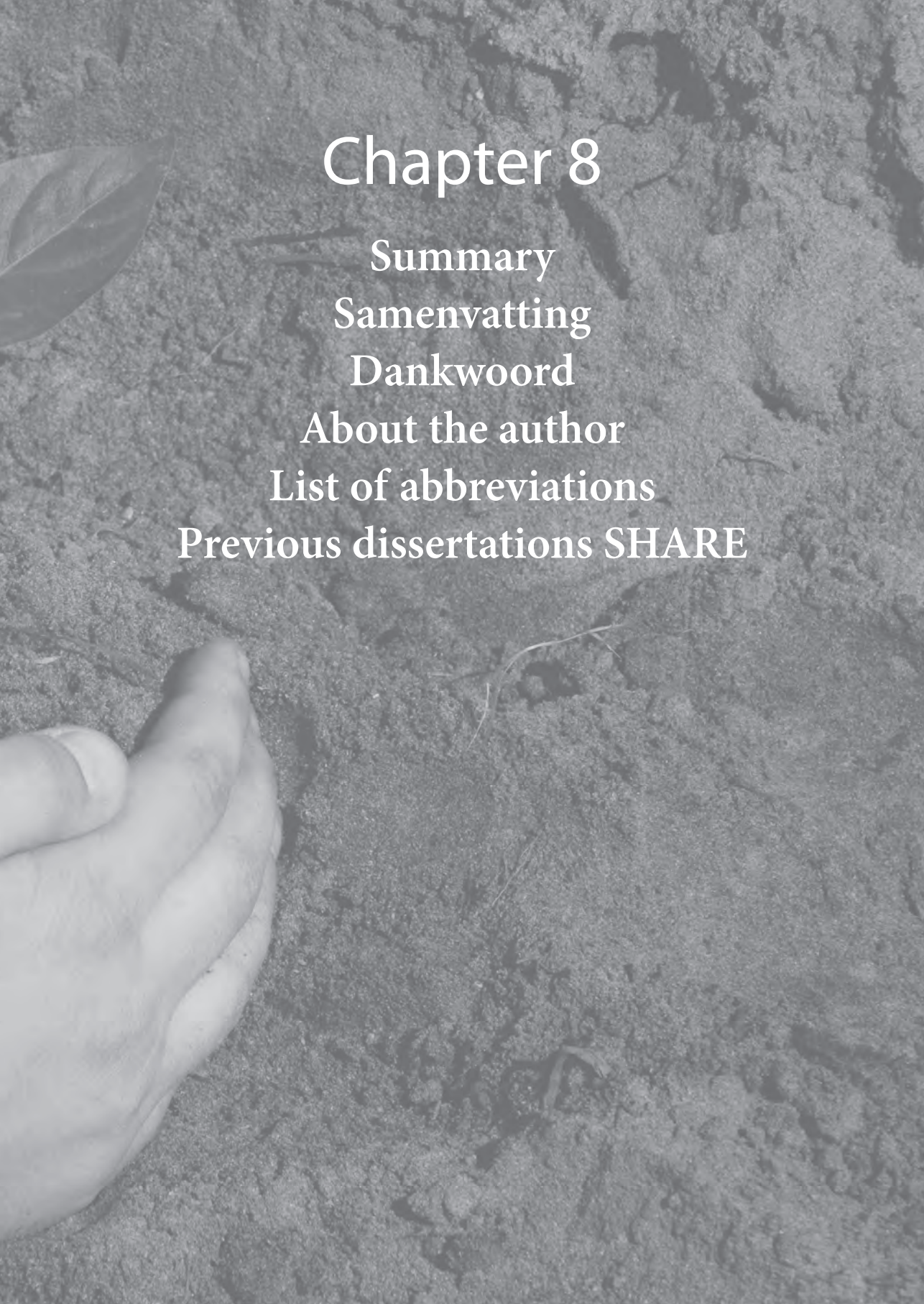

Chapter 8

Summary
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In foetal life and in early childhood, rapid developmental processes in the central nervous system enable a child to adapt to the demands of the environment. However, if children are exposed to early adversities, such as preterm birth and low socioeconomic status (SES), the normal neurodevelopmental processes may come under threat. Early adversities may cause permanent changes in brain and body functions, potentially affecting the foundations of mental and physical health. The main aim of this thesis was to determine the associations between moderate to late prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective. We translated this overall aim into the following five research questions:

1. Are moderate prematurity and low SES independently associated with developmental delay at pre-school age, or do they have joint effects?
2. What is the prevalence of behavioural and emotional problems in four-year-old, moderately preterm-born children, compared to the prevalence in full-term children?
3. Are moderate prematurity and low SES independently associated with behavioural and emotional problems at pre-school age, or do they have joint effects?
4. What is the prevalence of developmental delay co-occurring with behavioural and emotional problems in four-year-old, moderately preterm-born children compared to the prevalence in full-term controls?
5. Does poor emotion regulation in 18-year-olds predict the risk of coronary heart disease?

In Chapter 1 we describe the main topics of this thesis which led to the research questions mentioned above. In order to answer the first four research questions, we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP), a Dutch prospective cohort study designed to investigate the growth and development of children born preterm, with a special focus on moderate to late preterm children, born between 32 and 37 weeks of gestation. Participating children were recruited from thirteen preventive child healthcare centres in the Netherlands, in the years 2006 and 2007. For the fifth and final research question, we used data from a nationwide survey of over 45,000 Swedish males who were conscripted for compulsory military service in 1969/1970. This register-based study lent itself very well to examine the effects of emotional functioning in youth on cardiovascular

health in adulthood. More knowledge on this subject may help to unravel disease mechanisms that may have their roots in early child development.

In Chapter 2 we answer the question whether differences in SES could partly explain the association of moderate prematurity with developmental delay. We assessed SES on the basis of educational and occupational level of both parents and family income. The Ages and Stages Questionnaire (ASQ) was used to assess developmental delay of 926 moderately preterm and 544 full-term born children, at the age of four years. We computed scores for ASQ total problems and for the five developmental domains on which the overall score is based, i.e. fine and gross motor functioning, communication, problem-solving, and personal-social skills. Parents were asked to evaluate whether their child had achieved certain milestones on these domains. We found that prevalence rates for overall developmental delay were 12.5%, 7.8%, and 5.6% in moderately preterm-born children with low, intermediate, and high SES, respectively, and 7.2%, 4.0%, and 2.8% in term-born children, respectively. The risk of developmental delay increased more with decreasing SES than with decreasing gestational age: odds ratios (ORs) for a one standard deviation decrease were 1.62 (95% confidence interval [CI] 1.30-2.03) and 1.34 (95% CI 1.05-1.69), respectively. No interactions between SES and gestational age regarding their associations with developmental delay were found except for delay in communication skills. We concluded that low SES and moderate prematurity are separate risk factors with multiplicative effects on developmental delay. Therefore, moderately preterm-born children with low SES have a double jeopardy, which needs special attention in paediatric care.

In Chapter 3 we compare 995 moderately preterm and 577 full-term children regarding the prevalence of behavioural and emotional problems at four years of age, overall and by gender. Behavioural and emotional problems were measured using the Child Behavior Checklist (CBCL) for ages 1.5 to 5 years. The CBCL consists of 100 items on children's behaviour which are rated by parent as not true (0), somewhat/sometimes true (1), or very/often true (2). By summing the ratings for the items we computed seven syndrome scales, internalizing, externalizing, and total problems. Internalizing problems of the CBCL 1.5-5 consist of the syndrome scales emotionally reactive behaviour, anxious/depressed behaviour, somatic complaints, and withdrawn behaviour. Externalizing problems consist of the syndrome scales attention problems and aggressive behaviour. We found that moderately preterm-born children had poorer scores on all CBCL syndrome scales, and on the internalizing, externalizing, and total problems scales than

full-term controls. Prevalence rates of elevated externalizing problem scores were highest in boys (10.5%) and rates of internalizing problems were highest in girls (9.9%). Moderately preterm-born children were at greater risk for somatic complaints (OR 1.92, 95% CI 1.09-3.38), internalizing problems (OR 2.40, 95% CI 1.48-3.87), externalizing problems (OR 1.69, 95% CI 1.07-2.67), and total problems (OR 1.84, 95% CI 1.12-3.00). We concluded that moderately preterm-born children are more likely to have behavioural and emotional problems at pre-school age than full-term children. Therefore, moderately preterm-born children could be a potential target group for the prevention of mental health problems, since behavioural and emotional problems in early childhood tend to persist in later childhood and adolescence.

In Chapter 4 we assess to what extent low SES contributes to higher rates of behavioural and emotional problems in moderately preterm-born children. Therefore, we assessed separate and joint effects of moderate prematurity and SES in 915 moderately preterm and 543 full-term children. We found that moderately preterm-born children with low SES had significantly higher total problems-scores on the CBCL than those with high SES (11.3% vs. 5.1%). Each standard deviation decrease in SES was associated with 42% higher odds of elevated total problem-scores. No joint effects between SES and gestational age were found, which meant that lower gestational age independently added to the risk of behavioural and emotional problems. Furthermore, in line with the gender differences found in Chapter 3, girls were also more vulnerable to the effects of low SES than boys were. Especially the difference between moderately preterm-born girls from low and form high SES families was great: 13.0% of the low SES girls had elevated scores on total problems, compared to an average of 4.9% in all girls participating in the study. We concluded that moderate prematurity and low SES multiply the risk of behavioural and emotional problems and that the combination of these risk factors identifies children who could benefit the most from early interventions.

In Chapter 5 we aimed to determine the co-occurrence of developmental delay and behavioural and emotional problems in moderately preterm and full-term children. We hypothesized that moderately preterm-born children would have an increased risk of developmental delay co-occurring with behavioural and emotional problems, because of a biologic adversity in comparison with full-term children. A composite measure of co-occurrence was used combining the ASQ (an abnormal total or domain score) and the CBCL (a score above the 84th

percentile on total problems, internalizing or externalizing problems). Among moderately preterm-born children with overall developmental delay, behavioural and emotional problems were more prevalent than among full-term children, in particular regarding externalizing problems (34% vs. 24%). The risk of any type of co-occurrence was higher for moderately preterm than for full-term children (OR 1.86, 95% CI 1.14-3.03). Independent risk factors for co-occurrence were male gender, low SES, and low maternal age. From these findings we conclude that a quarter to a third of moderately preterm children with developmental delay also have behavioural and emotional problems. Therefore, in preventive child healthcare, paediatrics and child psychiatry, increased awareness is warranted for behavioural and emotional problems in moderate and late preterm-born children with developmental delay. We recommend to do further research in order to investigate the added value of addressing co-occurring neurodevelopmental problems at pre-school age.

In Chapter 6 we describe the role of young individual's emotional functioning for lifelong health. Specifically, we investigated the association between emotion regulation, which is one dimension of emotional functioning, and the long-term risk of coronary heart disease. The study comprised a population of 46,393 men who were conscripted for compulsory military service in Sweden, over 40 years ago. Psychologists assessed emotion regulation at conscription (age 18 to 20 years), in a 20-30 minutes-long semi-structured interview. The psychologists were instructed to ask the conscripts how they emotionally responded to important situational-dependent events (e.g. in the family, at school or at work) which they had experienced in childhood and adolescence. The results showed that 2,456 incident cases of coronary heart disease had occurred, after 38 years of follow-up (from 1971 until 2009). We found that men with poor emotion regulation skills had an increased risk of coronary heart disease (hazard ratio [HR] 1.31, 95% CI 1.18-1.45), after adjustment for childhood socioeconomic position, anxiety, depression, and parental history of coronary heart disease. Full adjustment for lifestyle-associated factors, e.g. smoking, attenuated the HR to 1.08 (95% CI 0.97-1.21). In stratified analyses, the fully adjusted HR for poor emotion regulation remained increased among men with a parental history of coronary heart disease (HR 1.49, 95% CI 1.11-2.01). We concluded that in the total study population poor emotion regulation was associated with coronary heart disease only via lifestyle-associated factors. Mediators of the association were smoking, education, and

cardiorespiratory fitness. Specifically in men with a parental history of coronary heart disease, poor emotion regulation in adolescence directly predicted the long-term risk of coronary heart disease.

Finally, in Chapter 7 we discuss the main findings of this thesis. From our results it follows that the combined biological and social risk of moderately preterm-born children with low SES translates into a substantial increased risk for developmental delay and behavioural and emotional problems. This implies that increased awareness is warranted for the relatively large group of moderately preterm-born children with low family SES. Regarding this implication, we recommend to refine the current multidisciplinary guideline concerning the early identification of developmental and psychosocial problems in preterm-born children. Professionals should know which children are most at risk, since the majority of moderately preterm-born children, approximately 80% to 90% will not have significant developmental or psychosocial problems. In addition, child healthcare professionals should be aware of the high probability of co-occurring behavioural and emotional problems in moderately preterm children with developmental delay.

Our findings also provide more insight into the pathways via which moderate prematurity and low SES lead to neurodevelopmental problems and via which emotion regulation may promote long-term health. Further research is needed to reveal the clinical implications of these insights and should be focused on a better understanding of: 1) associations between antenatal maternal stress, low SES, preterm birth, and neurodevelopmental problems, 2) the effectiveness of early interventions in moderately preterm-born children with low SES and/or those with multiple developmental and behavioural problems, 3) the pathophysiology of specific neurodevelopmental problems seen in moderately preterm-born and low SES children, and 4) the pathways between children's emotion regulation skills, affective disorders and coronary heart disease. Summarizing, this thesis shows that moderate prematurity and low SES have multiplicative risks of pre-school neurodevelopmental problems and that early acquired social-emotional competencies may promote long-term health.

Samenvatting

Tijdens het foetale leven en in de vroege kindertijd vinden snelle ontwikkelingsprocessen plaats in het centrale zenuwstelsel om een kind voor te bereiden op het leven buiten de baarmoeder. Wanneer kinderen echter worden blootgesteld aan ongunstige omstandigheden, zoals vroeggeboorte en een lage sociaaleconomische status (SES), kunnen deze ontwikkelingsprocessen verstoord worden. Vooral in de eerste levensjaren zou een dergelijke verstoring kunnen leiden tot blijvende veranderingen in hersenfuncties en regelsystemen van het lichaam, oftewel in fundamenten van psychische en lichamelijke gezondheid. Het doel van dit proefschrift was om de associaties te onderzoeken tussen matige tot late vroeggeboorte, SES en ontwikkelings- en gedragsproblemen op voorschoolse leeftijd, en om onderliggende neurologische processen te plaatsen in het kader van een levensloopperspectief. Dit algemene doel leidde tot de volgende vijf onderzoeksvragen:

1. Hebben matige vroeggeboorte en lage SES onafhankelijke associaties met ontwikkelingsachterstand op voorschoolse leeftijd of zijn er gemeenschappelijke effecten?
2. Wat is de prevalentie van gedrags- en emotionele problemen in matig te vroeg geboren kinderen op 4-jarige leeftijd, in vergelijking met de prevalentie in à terme geboren kinderen?
3. Hebben matige vroeggeboorte en lage SES onafhankelijke associaties met gedrags- en emotionele problemen op voorschoolse leeftijd of zijn er gemeenschappelijke effecten?
4. Wat is de prevalentie van het gelijktijdig voorkomen van ontwikkelingsachterstand en gedrags- en emotionele problemen op 4-jarige leeftijd in matig te vroeg geboren kinderen vergeleken met à terme geboren kinderen?
5. Voorspellen beperkte emotieregulatie-vaardigheden van 18-jarigen het risico op coronaire hartziekte?

In hoofdstuk 1 beschrijven we de belangrijkste onderwerpen van dit proefschrift die de basis vormen van bovenstaande onderzoeksvragen. Om de eerste vier onderzoeksvragen te beantwoorden, hebben we gebruik gemaakt van gegevens van de Pinkeltje studie, in het Engels aangeduid als 'Longitudinal Preterm Outcome Project' (LOLLIPOP). Deze prospectieve cohortstudie werd opgezet om de groei en ontwikkeling van te vroeg geboren kinderen te onderzoeken, met een speciale focus op kinderen die matig tot laat prematuur geboren zijn, dat wil zeggen tussen

32 en 37 weken zwangerschapsduur. Deelnemende kinderen werden geworven via dertien preventieve jeugdgezondheidszorginstellingen in Nederland, in 2006 en 2007. Voor de vijfde en laatste onderzoeksvraag gebruikten we de gegevens van een Zweeds onderzoek met informatie over meer dan 45.000 mannen die waren opgeroepen voor verplichte militaire dienst in 1969 en 1970. Deze studie leende zich er goed voor om te onderzoeken of het emotioneel functioneren van de toen 18-jarige mannen invloed heeft gehad op hun latere cardiovasculaire gezondheid. Deze kennis zou kunnen helpen bij het ontrafelen van ziektemechanismen die hun oorsprong hebben in de vroege sociaal-emotionele ontwikkeling.

Hoofdstuk 2 richt zich op de vraag of verschillen in SES (deels) kunnen verklaren waarom er een samenhang is tussen matige vroeggeboorte en ontwikkelingsachterstand. We stelden de SES vast op basis van het opleidings- en beroepsniveau van beide ouders en het gezinsinkomen. De Ages en Stages Questionnaire (ASQ) gebruikten we om ontwikkelingsachterstand vast te stellen in 926 matig prematuur en 544 à terme geboren kinderen, op de leeftijd van vier jaar. We berekenden scores voor ASQ totale problemen en voor de vijf ontwikkelingsdomeinen waarop de totale probleemscore is gebaseerd, dat wil zeggen fijne motoriek, grove motoriek, communicatie, probleemoplossende vaardigheden en persoonlijk-sociale vaardigheden. Aan ouders werd gevraagd om te beoordelen of hun kind bepaalde mijlpalen van deze ontwikkelingsdomeinen had bereikt. We vonden dat algehele ontwikkelingsachterstand meer voorkwam naarmate de SES lager was, in beide groepen. De betreffende prevalentiecijfers voor kinderen met een lage, gemiddelde en hoge SES waren respectievelijk 12,5%, 7,8% en 5,6% in matig te vroeg geboren kinderen en 7,2%, 4,0% en 2,8% in à terme geboren. Het risico op ontwikkelingsachterstand nam meer toe naarmate de SES lager was dan naarmate de zwangerschapsduur lager was. Odds ratio's (OR's) voor één standaarddeviatie afname waren respectievelijk 1,62 (95% betrouwbaarheidsinterval [BI] 1,30-2,03) en 1,34 (95% BI 1,05-1,69). Interactie-effecten tussen SES en zwangerschapsduur werden alleen gevonden in relatie tot communicatieve vaardigheden. We concludeerden dat lage SES en matige vroeggeboorte afzonderlijk werkende risicofactoren zijn met multiplicatieve effecten op ontwikkelingsachterstand. Matig te vroeg geboren kinderen met een lage SES hebben daarom een substantieel grotere kans op ontwikkelingsachterstand dan kinderen met slechts één van beide risicofactoren. Dit vereist speciale aandacht in de kindergeneeskunde en jeugdgezondheidszorg.

In hoofdstuk 3 onderzoeken we de prevalentie van gedrags- en emotionele problemen op 4-jarige leeftijd in 995 matig te vroeg en 577 à terme geboren kinderen, in totaal en afzonderlijk voor jongens en meisjes. Gedrags- en emotionele problemen werden gemeten met behulp van de Child Behavior Checklist (CBCL) voor kinderen van 1,5 tot 5 jaar. De CBCL bestaat uit 100 items over gedrag van kinderen die worden beoordeeld door de ouders als helemaal niet aan de orde (0), een beetje of soms (1), of duidelijk of vaak (2). Door het optellen van de scores voor bepaalde items kunnen scores op zeven syndroomschalen en op internaliserende, externaliserende en totale problemen worden berekend. Internaliserende problemen van de CBCL 1.5-5 zijn een optelling van de scores op de syndroomschalen emotioneel reactief gedrag, angstig of depressief gedrag, somatische klachten en teruggetrokken gedrag. Externaliserende problemen zijn een optelling van de scores op de syndroomschalen aandachtsproblemen en agressief gedrag. We vonden dat matig te vroeg geboren kinderen slechtere scores hadden op alle CBCL syndroomschalen en op internaliserende, externaliserende en totale problemen ten opzichte van à terme geboren kinderen. Prevalentiecijfers van externaliserende problemen waren het hoogst bij jongens (10,5%) en die van internaliserende problemen bij meisjes (9,9%). Matig te vroeg geboren kinderen hadden een groter risico op somatische klachten (OR 1,92, 95% BI 1,09-3,38), internaliserende problemen (OR 2.40, 95% BI 1,48-3,87), externaliserende problemen (OR 1,69, 95% BI 1,07-2,67), en totale problemen (OR 1,84, 95% BI 1,12-3,00). We concludeerden dat matig te vroeg geboren kinderen meer kans hebben op gedrags- en emotionele problemen op voorschoolse leeftijd dan à terme geboren kinderen. Matig te vroeg geboren kinderen zijn daarom een potentiële doelgroep voor de preventie van psychosociale problemen, omdat gedrags- en emotionele problemen in de vroege jeugd vaak een voorbode zijn van psychosociale problemen in de latere kindertijd en adolescentie.

Hoofdstuk 4 richt zich op de vraag in hoeverre lage SES bijdraagt aan de hogere prevalentie van gedrags- en emotionele problemen bij matig te vroeg geboren kinderen. Daarom onderzochten we de afzonderlijke en gecombineerde effecten van matige vroeggeboorte en SES in 915 matig te vroeg geboren en 543 à terme geboren kinderen. We vonden dat matig te vroeg geboren kinderen met een lage SES significant vaker een verhoogde totale probleemscore hadden op de CBCL dan kinderen met een hoge SES (11,3% versus 5,1%). Elke standaarddeviatie daling in SES hing samen met een 42% hogere odds op een afwijkende score op totale problemen. Er werden geen interactie-effecten tussen SES en zwangerschapsduur

gevonden. Dit betekent dat matige vroeggeboorte extra risico geeft op gedrags- en emotionele problemen, los van de effecten van lage SES. Bovendien vonden wij, in lijn met de sekseverschillen die beschreven werden in hoofdstuk 3, dat met name meisjes gevoelig waren voor de effecten van matige vroeggeboorte en lage SES: 13,0% van de lage SES meisjes had afwijkende scores op de totale problemen, in vergelijking met gemiddeld 4,9% van alle meisjes die deelnamen aan de studie. We concludeerden dat de risico's van matige vroeggeboorte en lage SES wat betreft gedrags- en emotionele problemen vermenigvuldigen en dat de combinatie van deze risicofactoren die kinderen identificeert die veel profijt zouden kunnen hebben van vroegtijdige interventies.

Hoofdstuk 5 richt zich op de vraag hoe vaak ontwikkelingsachterstand gepaard gaat met gedrags- en emotionele problemen, in matig te vroeg geboren kinderen en in à terme geboren kinderen. Onze hypothese was dat matig te vroeg geboren kinderen een verhoogd risico hebben op het gelijktijdig voorkomen van ontwikkelingsachterstand en gedrags- en emotionele problemen, vanwege een biologische achterstand ten opzichte van à terme geboren kinderen. We gebruikten een samengestelde maat voor het bepalen van gelijktijdig voorkomen van ontwikkelings- en gedragsproblemen door een combinatie van scores op de ASQ (een abnormale totaal- of domeinscore) en de CBCL (een score boven het 84ste percentiel op totale problemen, internaliserende en externaliserende problemen). Bij matig te vroeg geboren kinderen met een algehele ontwikkelingsachterstand kwamen gedrags- en emotionele problemen vaker voor dan bij à terme geboren kinderen, in het bijzonder geldend voor externaliserende problemen (34% vs. 24%). Het risico op verschillende combinaties van ontwikkelings- en gedragsproblemen was hoger voor matig te vroeg geboren dan à terme geboren kinderen (OR 1,86, 95% BI 1,14-3,03). Onafhankelijke risicofactoren voor het gelijktijdig voorkomen van ontwikkelingsachterstand en gedrags- en emotionele problemen waren mannelijk geslacht, een lage SES en jonge leeftijd van de moeder. Uit deze bevindingen concludeerden wij dat een kwart tot een derde van de matig te vroeg geboren kinderen met een ontwikkelingsachterstand tevens gedrags- en emotionele problemen heeft. In de preventieve jeugdgezondheidszorg, kindergeneeskunde en kinderpsychiatrie is daarom extra aandacht nodig voor het gelijktijdig bestaan van gedrags- en emotionele problemen naast reeds gesignaleerde ontwikkelingsachterstand bij matig te vroeg geboren kinderen. Nader onderzoek is nodig om de toegevoegde waarde te bepalen van vroegsignalering op zowel ontwikkelingsachterstand als gedragsproblemen.

In hoofdstuk 6 beschrijven we de invloed van emotioneel functioneren op jonge leeftijd op cardiale gezondheid op de lange termijn. We onderzochten de samenhang tussen emotieregulatie (een dimensie van emotioneel functioneren) en het risico op coronaire hartziekten. Het onderzoek bestond uit een populatie van 46.393 mannen die waren opgeroepen voor verplichte militaire dienst in Zweden, meer dan 40 jaar geleden. Psychologen beoordeelden destijds de emotieregulatie-vaardigheden bij de screening voor de dienstplicht toen de dienstplichtigen 18 tot 20 jaar oud waren. Dit deden zij aan de hand van een 20-30 minuten durend semigestructureerd interview. De psychologen werden geïnstrueerd aan de dienstplichtigen te vragen hoe ze emotioneel reageerden op belangrijke situatie-afhankelijke gebeurtenissen (bijvoorbeeld in de familie, op school of op het werk) die zij hadden ervaren in de kindertijd en adolescentie. De resultaten toonden aan dat er 2456 gevallen van coronaire hartziekte hadden plaatsgevonden na 38 jaar follow-up (van 1971 tot 2009). We vonden dat mannen met slechte emotieregulatie-vaardigheden een verhoogd risico hadden op coronaire hartziekten (hazard ratio [HR] 1,31, 95% BI 1,18-1,45), na correctie voor SES op kinderleeftijd, angst, depressie, en familiaire belasting voor coronaire hartziekte. Volledige correctie voor aan levensstijl geassocieerde factoren, zoals roken, verzwakte de HR tot 1,08 (95% BI 0,97-1,21). In gestratificeerde analyses bleek dat de volledig gecorrigeerde HR verhoogd bleef bij de mannen met slechte emotieregulatie-vaardigheden én een familiaire belasting voor coronaire hartziekte (HR 1,49, 95% BI 1,11-2,01). We concludeerden dat slechte emotieregulatie-vaardigheden geassocieerd zijn met coronaire hartziekten, voornamelijk via de invloed van leefstijlfactoren. Mediatoren van de gevonden associatie waren roken, opleidingsniveau en lichamelijke conditie ('cardiorespiratory fitness'). Bij mannen met een familiaire belasting voor coronaire hartziekten werd ook een directe associatie gevonden tussen slechte emotieregulatie-vaardigheden en een hoger risico op coronaire hartziekten.

Ten slotte biedt hoofdstuk 7 een bespreking van de belangrijkste bevindingen van dit proefschrift. Uit onze resultaten volgt dat de gecombineerde biologische en sociale risico's van matig te vroeg geboren kinderen met een lage SES vertaald worden in een substantieel hoger risico op ontwikkelingsachterstand en gedrags- en emotionele problemen. Dit betekent dat er meer aandacht nodig is voor deze problematiek in de relatief grote groep van matig prematuur geboren kinderen met een lage SES. Ten aanzien van deze implicatie lijkt het gewenst om de huidige multidisciplinaire richtlijn met betrekking tot de vroegtijdige opsporing

van ontwikkelingsstoornissen en psychosociale problemen bij te vroeg geboren kinderen aan te scherpen. Het is belangrijk dat professionals weten welke kinderen het meeste risico lopen, omdat de meerderheid van de matig prematuur geboren kinderen, ongeveer 80% tot 90%, geen significante ontwikkelings- of psychosociale problemen heeft. Bovendien is er meer aandacht nodig voor het frequent voorkomen gedrags- en emotionele problemen bij matig te vroeg geboren kinderen met een ontwikkelingsachterstand.

Onze bevindingen geven ook meer inzicht in de mechanismen waardoor matige vroeggeboorte en lage SES kunnen leiden tot ontwikkelings- en gedragsproblemen en waardoor emotieregulatie-vaardigheden de gezondheid op de lange termijn kunnen beïnvloeden. Echter, nader onderzoek is nodig om deze mechanismen te verhelderen en om de consequenties voor de klinische zorg van de resultaten uit dit proefschrift duidelijker te krijgen. Vervolgonderzoek kan zich bijvoorbeeld richten op een beter begrip van: 1) de samenhang tussen prenatale maternale stress, lage SES, vroeggeboorte en ontwikkelings- en gedragsproblemen, 2) de effectiviteit van vroegtijdige interventies bij matig te vroeg geboren kinderen met een lage SES en/of met meerdere ontwikkelings- en gedragsproblemen, 3) de pathofysiologie van de specifieke ontwikkelingsproblemen die worden gezien bij matig te vroeg geboren en lage SES kinderen, en 4) verklaringen voor de samenhang tussen emotieregulatie-vaardigheden van kinderen, affectieve stoornissen en coronaire hartziekten. Samenvattend laat dit proefschrift zien dat matige vroeggeboorte en lage SES gecombineerd substantiële effecten hebben op ontwikkelingsachterstand en gedrags- en emotionele problemen op 4-jarige leeftijd en dat vroeg verworven sociaal-emotionele competenties bevorderend kunnen zijn voor de latere cardiovasculaire gezondheid.

Dankwoord

Zonder de medewerking en steun van velen zou dit proefschrift nooit geschreven zijn. Graag wil ik iedereen bedanken die op enige manier betrokken is geweest bij het onderzoek. Enkelen wil ik hier in het bijzonder noemen.

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About the author

Marieke Potijk was born on May 17th 1988 in Heerenveen, the Netherlands. She grew up in the village of Sint Nicolaasga, in a family of four children. After graduation from high school, she moved to Groningen to study Medicine. In 2009 she received her Bachelor's degree. At that time she started a research project at the department of Neonatology, University Medical Center Groningen (UMCG), resulting in a master thesis about the effects of antenatal and perinatal factors on developmental delay in moderately preterm-born children. This experience further stirred up her interest in scientific research, and she decided to write an MD/PhD application, resulting in this thesis. During the years of research and clinical internships, her interest in preventive child healthcare and child psychiatry increased. Therefore, in 2013 she finished medical school with a specialization internship in psychiatry. After graduation, she went to Sweden for a research collaboration with colleagues from the public health department at Karolinska Institutet, Stockholm. In June 2014 she returned, and soon thereafter she started to combine her research activities with a job as medical doctor at the University Center for Child and Youth Psychiatry (Accare) in Groningen.

List of abbreviations

ASQ	Ages and Stages Questionnaire
CBCL	Child Behavior Checklist
CHD	Coronary Heart Disease
DOHaD	Developmental Origins of Health and Disease
LOLLIPOP	Longitudinal Preterm Outcome Project
MP	Moderately Preterm-born
PCH	Preventive Child Healthcare
SES	Socioeconomic Status

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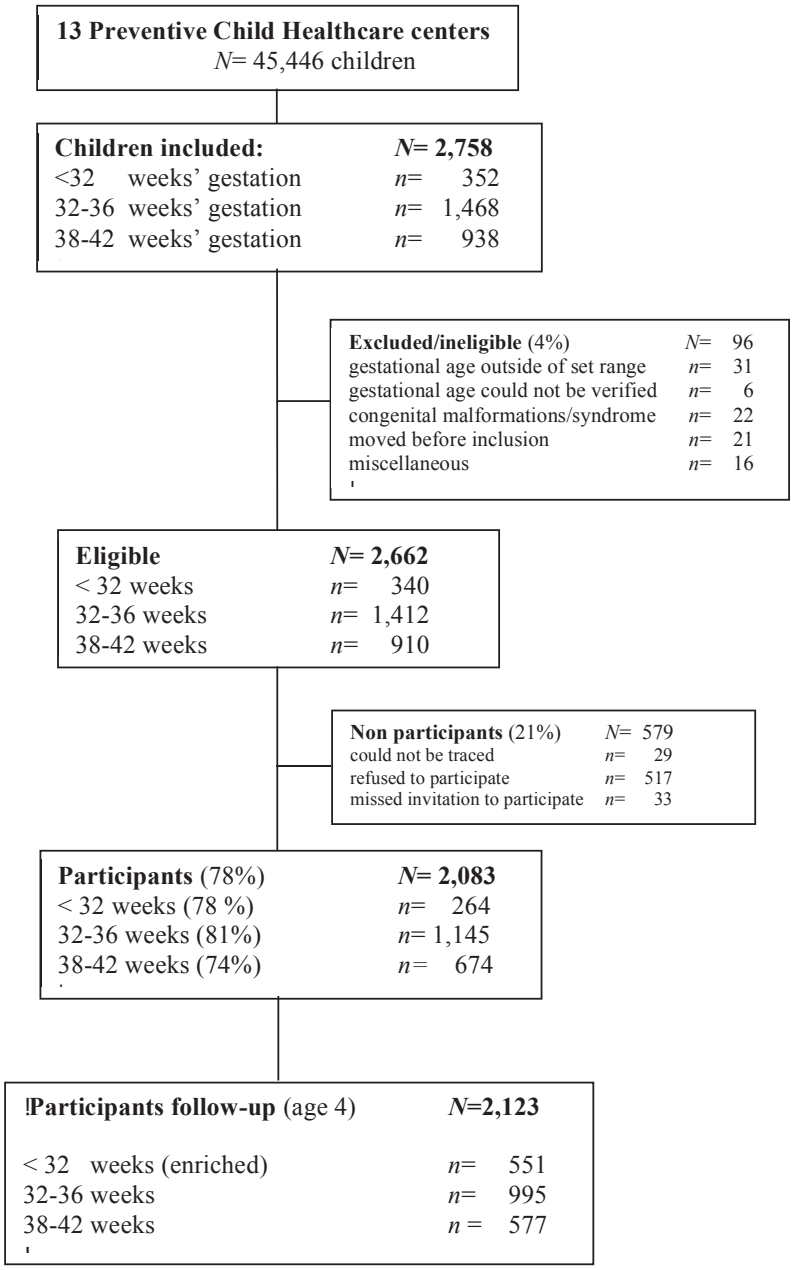
Appendix 1

Flowchart of sampling procedures in the LOLLIPOP study



Appendix 2

Ages and Stages Questionnaire (ASQ)

48 maanden ◆ 4 jaar
ASQ vragenlijst

Op de volgende pagina's worden vragen gesteld over activiteiten van kinderen. Uw kind doet wellicht al sommige van de omschreven activiteiten, maar het kan ook zijn dat uw kind hier nog niet mee begonnen is. Dat is normaal, de vragenlijst is gemaakt voor kinderen van 4 jaar, terwijl uw kind op dit. moment nog geen vier jaar oud is. Vul bij elk item in of uw kind de betreffende activiteit *regelmatig*, *soms* of *nog niet* doet.

Belangrijke zaken om te bedenken:

- Wees er zeker van dat uw kind elke activiteit heeft geprobeerd, voordat u het antwoord aankruist.
- Maak van het doen van de testjes een leuk spel voor uzelf en uw kind. Zo kunt u beiden aan het invullen van de vragenlijst ook nog plezier beleven.
- Zorg ervoor dat uw kind uitgerust is en zin heeft om te spelen.
- Neem deze vragenlijst mee in de de bijgevoegde antwoordenvelop bij uw bezoek aan het consultaitebureau.
- Als u vragen of zorgen heeft over uw kind of over de vragenlijst, neemt u dan contact op met uw consultatiebureau-arts.
- Op de leeftijd van 5 jaar sturen wij u weer een vragenlijst, maar dan voor kinderen voor 5 jaar, u zult zien dat uw kind dan alweer heel veel andere dingen kan dan nu.

Als er in de vragen sprake is van het woord *hij* dan wordt daar uiteraard *hij* of *zij* bedoeld.

		JA	SOMS	NOG NIET	
COMMUNICATIE	probeer elke activiteit samen met uw kind uit.				
1.	Kan uw kind minimaal drie items noemen uit een alledaagse categorie? Bijvoorbeeld als u vraagt: 'Kun je me een aantal dingen vertellen die je kunt eten?' Antwoordt uw kind bijvoor- beeld: 'Koekjes, eieren, pap'? Of als u vraagt: 'Kun je een paar dieren noemen'? Antwoordt uw kind bijvoorbeeld: 'Koe, hond en olifant'.	☐	☐	☐	—
2.	Kan uw kind de volgende vragen beantwoorden? 'Wat doe je als je honger hebt'? (Goede antwoorden bevatten: enkele van de volgende woorden of zinnetjes) eten krijgen, eten, iets te eten vragen. Schrijf hier het antwoord van uw kind: _____ 'Wat doe je als je moe bent'? (Goede antwoorden bevatten: een dutje doen, uitrusten, slapen, naar bed gaan, even liggen, zitten). Schrijf hier het antwoord van uw kind: _____ Kruis SOMS aan als uw kind slechts één vraag beantwoordt	☐	☐	☐	—
3.	Vertelt uw kind u ten minste twee dingen over alledaagse voorwerpen? Bijvoorbeeld als u vraagt: 'Vertel me iets over je bal', zegt het kind iets als:'Hij is rond; Ik gooi ermee; Hij is groot'?				—
4.	Gebruikt uw kind al vervoegingen , en meervoudsvormen in zinnen zoals; 'ik zie twee kip*pen*', en hij 'gooi*de* de bal'?	☐	☐	☐	—
5.	Kan uw kind drie instructies opvolgen, die ***niet*** bij elkaar horen? Zonder dat u hem helpt met aanwijzigingen en zonder herhaling van de vraag. Bijvoorbeeld: vraag uw kind 'Klap in je handen, loop naar de deur en ga zitten'.	☐	☐	☐	
6.	Maakt uw kind al complete zinnen. (bijvoorbeeld: een, de, het, en *ga of kom* in een zin)? 'Ik ga spelen in het park' ' Kom jij ook?'	☐	☐	☐	—
COMMUNICATIE TOTAAL					—
GROVE MOTORIEK	probeer iedere activiteit met uw kind				
1.	Kan uw kind een grote bal met twee handen vangen? Ga onge- veer anderhalve meter bij uw kind vandaan staan en gooi de bal naar uw kind. Probeer dit twee tot drie keer.	☐	☐	☐	—
2.	Kan uw kind zonder hulp op een glijbaan klimmen en zelf naar beneden glijden?	☐	☐	☐	—

		JA	SOMS	NOG NIET	
3.	Kan uw kind, terwijl hij stilstaat, bovenhands een bal gooien naar iemand die drie meter verderop staat? Om bovenhands te gooien moet uw kind zijn arm omhoog brengen tot schouderhoogte en de bal naar voren gooien. (De bal laten vallen, laten rollen of onder- hands gooien moet gescoord worden als NOG NIET).	☐	☐	☐	—
4.	Kan uw kind ten minste één keer op het linker- of rechterbeen op en neer springen, zonder daarbij zijn evenwicht te verliezen of om te vallen?	☐	☐	☐	—
5.	Kan uw kind vanuit stand een halve meter naar voren springen, waarbij hij met twee voeten afzet?	☐	☐	☐	—
6.	Kan uw kind, zonder zich aan iets vast te houden, 5 seconden op één been staan zonder zijn balans te verliezen en zijn andere voet op de grond te zetten? Uw kind mag dit twee tot drie keer proberen, voordat u deze vraag beantwoordt.	☐	☐	☐	—
GROVE MOTORIEK TOTAAL					—

FIJNE MOTORIEK	probeer iedere activiteit met uw kind				
1.	Kan uw kind een puzzel van zes stukjes in elkaar zetten? (Als u geen puzzel hebt, neem dan een hele pagina uit een tijdschrift en knip deze in 6 stukken. Kan uw kind deze goed terugleggen?)	☐	☐	☐	—
2.	Gebruik een kindvriendelijke schaar. Kan uw kind een stuk papier in de helft knippen in een min of meer rechte lijn, waarbij hij de schaar goed gebruikt? (Let goed op hoe uw kind de schaar gebruikt in verband met de veiligheid).	☐	☐	☐	—
3.	Laat uw kind naar onderstaande vormen kijken. Kan uw kind ten minste drie vormen natekenen op een groot stuk papier, met pen of potlood. De tekening van uw kind moet op het ontwerp van de vormen lijken, maar mogen een afwijkende afmeting hebben.	☐	☐	☐	—
	L + I O				
4.	Kan uw kind één of meer knopen losmaken? Uw kind mag zowel zijn eigen kleding als poppenkleding losmaken.	☐	☐	☐	—
5.	Kan uw kind mensen tekenen die ten minste drie van de volgende kenmerken hebben: hoofd, ogen, neus, mond, nek, haar, romp, armen, handen, benen of voeten?	☐	☐	☐	—
6.	Kleurt uw kind in een kleurboek meestal binnen de lijnen? Uw kind mag niet meer dan een halve centimeter buiten de lijnen bij het merendeel van de kleurplaat.	☐	☐	☐	—
FIJNE MOTORIEK TOTAAL					—

		JA	SOMS	NOG NIET	
PROBLEEM OPLOSSEND VERMOGEN	probeer iedere activiteit samen met uw kind uit.				
1.	Als u zegt, 'Zeg: vijf acht drie,' herhaalt uw kind dan alleen deze drie cijfers in de juiste volgorde? Herhaal deze cijfers zelf niet. Indien nodig, probeer dan een andere serie cijfers en zeg: 'Zeg zes negen twee'. Uw kind hoeft slechts één serie van drie cijfers juist te herhalen om antwoord JA aan te kruisen.	☐	☐	☐	—
2.	Als u vraagt: 'Welke cirkel is het kleinst?' Wijst uw kind dan de kleinste cirkel aan? Stel deze vraag zonder hulp aan te bieden door middel van aanwijzingen, gebaren maken of kijken naar de kleinste cirkel.	☐	☐	☐	—
	o o o				
3.	Volgt uw kind drie verschillende richtingen zoals 'onder', 'tussen', 'in het midden' zonder dat u daarbij aanwijzingen geeft? Vraag uw kind bijvoorbeeld 'een boek onder de bank te leggen'. Vraag hem daarna 'de bal tussen de stoelen te leggen' en 'de schoenen in het midden van de tafel te zetten'.	☐	☐	☐	—
4.	Als u een voorwerp laat zien en naar de kleur vraagt, benoemt uw kind dan vijf verschillende kleuren zoals rood, blauw, geel, oranje, zwart, wit of roze? Antwoord JA indien uw kind de vraag juist beantwoordt en vijf kleuren benoemt.	☐	☐	☐	—
5.	Verkleedt uw kind zich en speelt het toneel, doet het alsof hij iemand of iets anders is? Bijvoorbeeld, uw kind verkleed zich in andere kleren en doet alsof hij de moeder, vader, broer of zus is of een denkbeeldig dier of figuur.	☐	☐	☐	—
6.	Als u vijf voorwerpen voor uw kind plaatst; kan hij ze dan tellen, een, twee, drie, vier, vijf in de juiste volgorde? Stel deze vraag zonder hulp te bieden door aanwijzingen, gebaren of benoemen.	☐	☐	☐	—
PROBLEEMOPLOSSEN TOTAAL					—
PERSOONLIJK-SOCIAAL	Probeer iedere activiteit met uw kind				
1.	Kan uw kind zichzelf bedienen door eten uit een blik/pot [potje?] over te scheppen naar een bord door bestek te gebruiken? Bijvoorbeeld, kan uw kind met een grote lepel appelmoes uit een potje in een kom scheppen?	☐	☐	☐	—

		JA	SOMS	NOG NIET	
2.	Kan uw kind antwoord geven op ten minste vier van onderstaande vragen: a. voornaam b. achternaam c. leeftijd d. jongen of meisje e. woonplaats f. telefoonnummer De vragen die uw kind juist beantwoordt graag omcirkelen.	☐	☐	☐	—
3.	Kan uw kind zelfstandig zijn handen en gezicht met zeep wassen en afdrogen?	☐	☐	☐	—
4.	Kan uw kind de namen van twee of meer vriendjes noemen (broertjes of zusje niet meegerekend). Stel deze vraag zonder hulp te bieden door namen te noemen van andere vriendjes.	☐	☐	☐	—
5.	Kan uw kind zelfstandig tandpasta op zijn tandenborstel doen en zijn tanden poetsen. Het kan daarbij nodig zijn dat u controleert en nog moet napoetsen.	☐	☐	☐	—
6.	Kan uw kind zich zelfstandig uitkleden? (behalve: ?drukkers, knopen en ritsen).	☐	☐	☐	—
PERSOONLIJK-SOCIAAL TOTAAL					—

		JA	NEE	
OVERALL	Ouders en verzorgers kunnen onderstaande ruimte of de achterkant van deze pagina gebruiken voor aanvullende informatie of opmerkingen.			
1.	Denk u dat uw kind goed hoort?	☐	☐	
2.	Denkt u dat uw kind spreekt als andere kinderen van zijn leeftijd?	☐	☐	
3.	Begrijpt u het meest van wat uw kind zegt?	☐	☐	
4.	Denkt u dat uw kind loopt, rent en klimt als andere kinderen van zijn leeftijd?	☐	☐	
5.	Is bij een of bij beide ouders in de familiegeschiedenis sprake van doofheid of slechthorendheid in de kindertijd?	☐	☐	
6.	Heeft u zorgen over het gezichtsvermogen van uw kind?	☐	☐	
7.	Heeft u kind in de laatste maanden last van medische problemen?	☐	☐	
8.	Maakt u zich op enige manier zorgen over uw kind?	☐	☐	

Appendix 3

Child Behavior Checklist (CBCL)

Hieronder is een lijst met vragen over kinderen. Alle vragen gaan over hoe uw kind ***nu is of in de afgelopen 2 maanden is geweest***. Zet een kruisje in het hokje horend bij antwoord **2** als de vraag ***duidelijk of vaak*** bij uw kind past. Zet een kruisje in het hokje horend bij antwoord ***1*** als de vraag ***een beetje of soms*** bij uw kind past. Als de vraag ***helemaal niet*** bij uw kind past, zet dan een kruisje in het hokje horend bij antwoord **0**. Beantwoord alle vragen zo goed als u kunt, ook al lijken sommige vragen niet bij uw kind te passen.

0 = Helemaal niet **1 = Een beetje of soms** **2 = Duidelijk of vaak**

0	1	2		0	1	2	
☐	☐	☐	1. Pijnklachten (zonder medische oorzaak; **geen buikpijn of hoofdpijn**)	☐	☐	☐	27. Lijkt zich niet schuldig te voelen na zich misdragen te hebben.
☐	☐	☐	2. Doet te jong voor zijn/haar leeftijd.	☐	☐	☐	28. Wil het huis niet uit.
☐	☐	☐	3. Is bang om iets nieuws te proberen.	☐	☐	☐	29. Snel van streek als iets tegenzit
☐	☐	☐	4. Vermijdt anderen aan te kijken.	☐	☐	☐	30. Snel jaloers.
☐	☐	☐	5. Kan zich niet concentreren; kan niet lang de aandacht ergen bij houden.	☐	☐	☐	31. Eet of drinkt dingen die eigenlijk niet eetbaar of drinkbaar zijn – snoep **niet** meetellen (schrijf op):
☐	☐	☐	6. Kan niet stil zitten, is onrustig of hyperactief.				
☐	☐	☐	7. Kan er niet tegen wanneer dingen ergens anders staan.	☐	☐	☐	32. Is bang voor bepaalde dieren, situaties, of plaatsen, (schrijf op):
☐	☐	☐	8. Kan niet tegen wachten; alles moet nu gebeuren.	☐	☐	☐	33. Voelt zich snel beledigd of gekwetst.
☐	☐	☐	9. Kauwt op dingen die niet eetbaar zijn.	☐	☐	☐	34. Bezeert zich vaak; krijgt vaak ongelukken.
☐	☐	☐	10. Klampt zich vast aan volwassenen of is te afhankelijk.	☐	☐	☐	35. Vecht veel.
☐	☐	☐	11. Zoekt voortdurend hulp.	☐	☐	☐	36. Bemoeit zich met alles.
☐	☐	☐	12. Obstipatie; heeft geen ontlasting (zonder dat hij/zij ziek is).	☐	☐	☐	37. Raakt te veel overstuur wanneer hij/zij gescheiden wordt van zijn/haar ouders.
☐	☐	☐	13. Huilt veel.				
☐	☐	☐	14. Wreed tegen dieren.	☐	☐	☐	38. Heeft moeite met inslapen.
☐	☐	☐	15. Uitdagend	☐	☐	☐	39. Hoofdpijnen (zonder medische oorzaak).
☐	☐	☐	16. Wil in alles direct zijn/haar zin hebben.	☐	☐	☐	40. Slaat anderen.
☐	☐	☐	17. Vernielt eigen spullen.	☐	☐	☐	41. Houdt zijn/haar adem in.
☐	☐	☐	18. Vernielt spullen van gezinsleden of van andere kinderen.	☐	☐	☐	42. Doet dieren of mensen zonder opzet pijn.
☐	☐	☐	19. Diarree of dunnen ontlasting (zonder dat hij/zij ziek is).	☐	☐	☐	43. Ziet er ongelukkig uit zonder duidelijke reden.
☐	☐	☐	20. Ongehoorzaam	☐	☐	☐	44. Boze buien.
☐	☐	☐	21. Verstoord wanneer iets anders gaat dan hij/zij gewend is.	☐	☐	☐	45. Misselijk (zonder medische oorzaak).
☐	☐	☐	22. Wil niet alleen slapen.	☐	☐	☐	46. Zenuwachtige bewegingen of zenuwtrekken (schrijf op):
☐	☐	☐	23. Geeft geen antwoord wanneer anderen tegen hem/haar praten.	☐	☐	☐	47. Nerveus zenuwachtig of gespannen.
☐	☐	☐	24. Eet niet goed (schrijf op):	☐	☐	☐	48. Nachtmerries.
				☐	☐	☐	49. Eet te veel.
☐	☐	☐	25. Kan niet opschieten met andere kinderen.	☐	☐	☐	50. Is erg moe.
				☐	☐	☐	51. Is in paniek zonder duidelijke reden.
☐	☐	☐	26. Kan geen pret maken; doet als een kleine volwassene.	☐	☐	☐	52. Pijnlijke ontlasting (zonder medische oorzaak).
				☐	☐	☐	53. Valt mensen lichamelijk aan.

GEDRAG EN EIGENSCHAPPEN

0 = Helemaal niet (voor zover U weet) 1 = Een beetje of soms 2 = Duidelijk of vaak

0	1	2		0	1	2	
☐	☐	☐	54. Pulkt aan neus, huid of aan iets anders van het lichaam (schrijf op):	☐	☐	☐	76. Spraakprobleem (schrijf op):
☐	☐	☐	55. Speelt te veel met eigen geslachtsdelen.	☐	☐	☐	77. Staart voor zich uit of lijkt volledig in beslag genomen.
☐	☐	☐	56. Onhandig of stuntelig.	☐	☐	☐	78. Buikpijn of krampen (zonder medische oorzaak).
☐	☐	☐	57. Oogproblemen (zonder medische oorzaak) (schrijf op):	☐	☐	☐	79. Snelle wisselingen tussen verdriet en opwinding.
☐	☐	☐	58. Straffen verandert zijn/haar gedrag niet.	☐	☐	☐	80. Vreemd gedrag (schrijf op):
☐	☐	☐	59. Gaat snel over van de ene bezigheid naar de andere.	☐	☐	☐	81. Koppig, stuurs of prikkelbaar.
☐	☐	☐	60. Huiduitslag of andere huidproblemen (zonder medische oorzaak).	☐	☐	☐	82. Stemming en gevoelens veranderen plotseling.
☐	☐	☐	61. Weigert om te eten.	☐	☐	☐	83. Mokt veel.
☐	☐	☐	62. Weigert om actieve spelletjes te spelen.	☐	☐	☐	84. Praat of schreeuwt in slaap.
☐	☐	☐	63. Bonkt steeds met hoofd of wiegt met lichaam.	☐	☐	☐	85. Driftbuien of snel driftig
☐	☐	☐	64. Verzet zich 's avonds met naar bed gaan.	☐	☐	☐	86. Overdreven netjes of te schoon.
☐	☐	☐	65. Verzet zich tegen zindelijk worden (schrijf op):	☐	☐	☐	87. Te angstig of te bang.
☐	☐	☐	66. Schreeuwt veel.	☐	☐	☐	88. Werkt niet mee.
☐	☐	☐	67. Lijkt niet te reageren op liefde of genegenheid.	☐	☐	☐	89. Weinig actief; beweegt zich langzaam of te weinig energie.
☐	☐	☐	68. Schaamt zich gauw of voelt zich niet op zijn/haar gemak.	☐	☐	☐	90. Ongelukkig, verdrietig of depressief.
☐	☐	☐	69. Egoistisch; wil niet delen.	☐	☐	☐	91. Meer dan gewoon luidruchtig
☐	☐	☐	70. Toont weinig liefde of genegenheid voor anderen.	☐	☐	☐	92. Van streek door onbekende mensen of situaties.
☐	☐	☐	71. Toont weinig belangstelling voor dingen om zich heen.	☐	☐	☐	93. Overgeven (zonder medische oorzaak).
☐	☐	☐	72. Toont te weinig angst om zich te bezeren	☐	☐	☐	94. Wordt 's nachts vaak wakker.
☐	☐	☐	73. Te verlegen of timide.	☐	☐	☐	95. Loopt weg.
☐	☐	☐	74. Slaapt overdag en/of 's nachts minder dan de meeste kinderen (schrijf op):	☐	☐	☐	96. Wil veel aandacht.
☐	☐	☐	75. Smeert of speelt met ontlasting	☐	☐	☐	97. Zeurend.
				☐	☐	☐	98. Teruggetrokken; gaat niet met anderen om.
				☐	☐	☐	99. Maakt zich zorgen.
							100. Schrijf hier ieder ander probleem op dat het kind heeft en dat hierboven nog niet genoemd is.